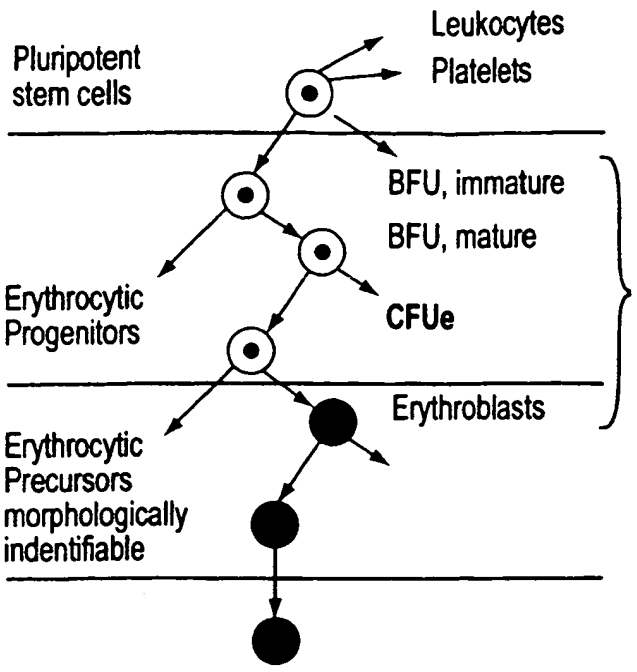
## Erythropoiesis




EPO is believed to

- Stimulate the proliferation and differentiation of committed erythroid cells
- Prevent the apoptosis of erythrocytic progenitors
- Increase the viability of erythrocytes

FIG. 1

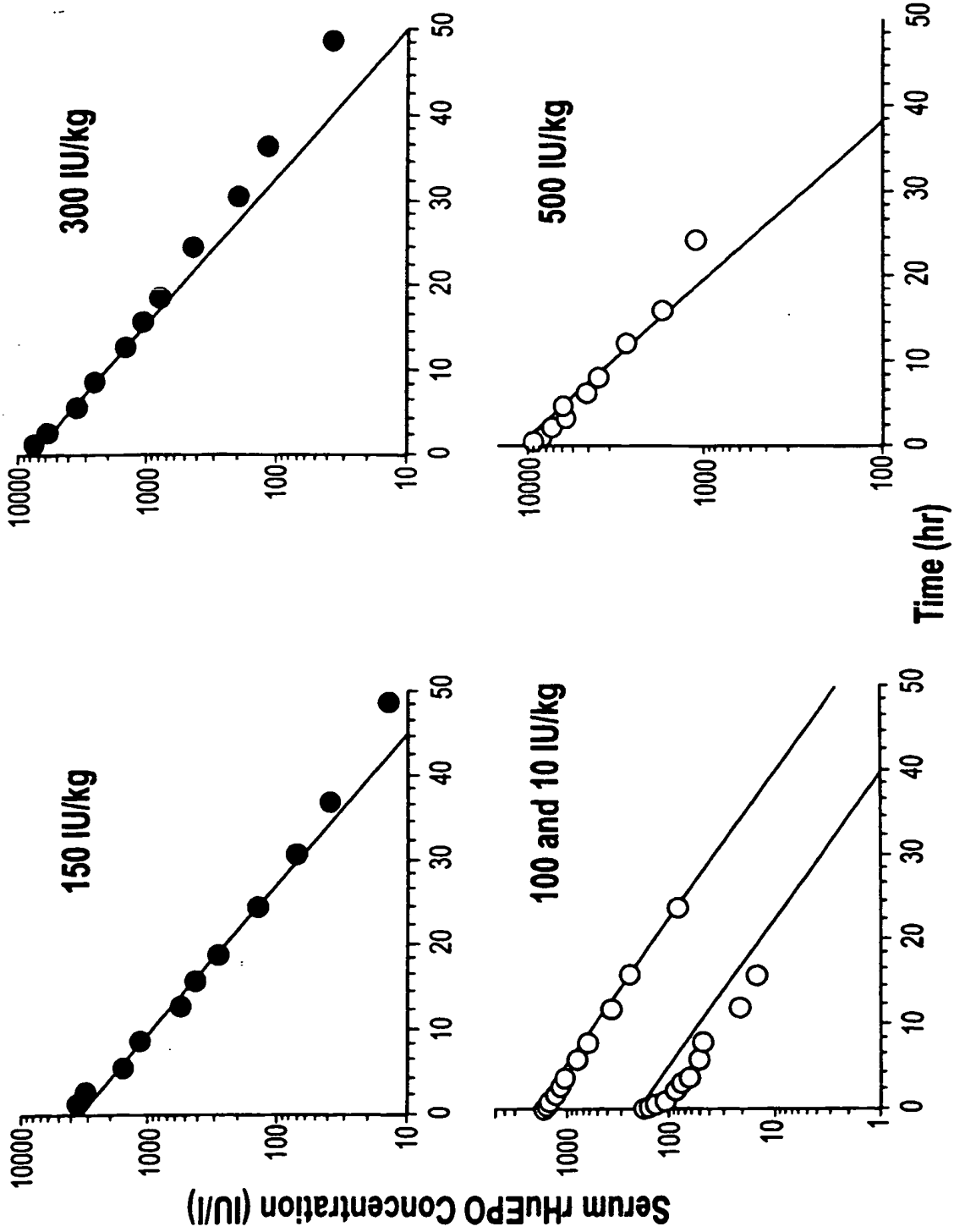

300 IU/kg
500 IU/kg
150 IU/kg
100 and 10 IU/kg
Serum rHuEPO Concentration (IU/l)
Time (hr)

FIG. 2

# PHARMACOKINETIC PARAMETERS FOR INTRAVENOUS AND SUBCUTANEOUS EPO DOSES

| PARAMETER | ESTIMATE | CV% |
|---|---|---|
| Vmax (IU/hr) | 138.5 | |
| Km (IU/l) | 20940 | |
| Vd (l/kg) | 0.0558 | |
| ka ($hr^{-1}$) | 0.0219 | 4.836 |
| Fr | 0.131 | 7.291 |
| $\tau$ (Lower doses, hr) | 44 | |
| $\tau$ (Higher doses, hr) | 60 | |

FIG. 3

## PHARMACOKINETIC MODEL

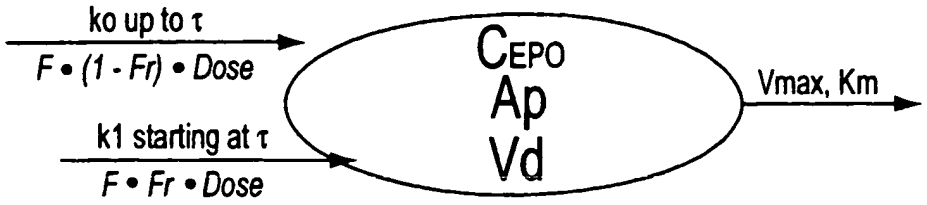



FIG. 4

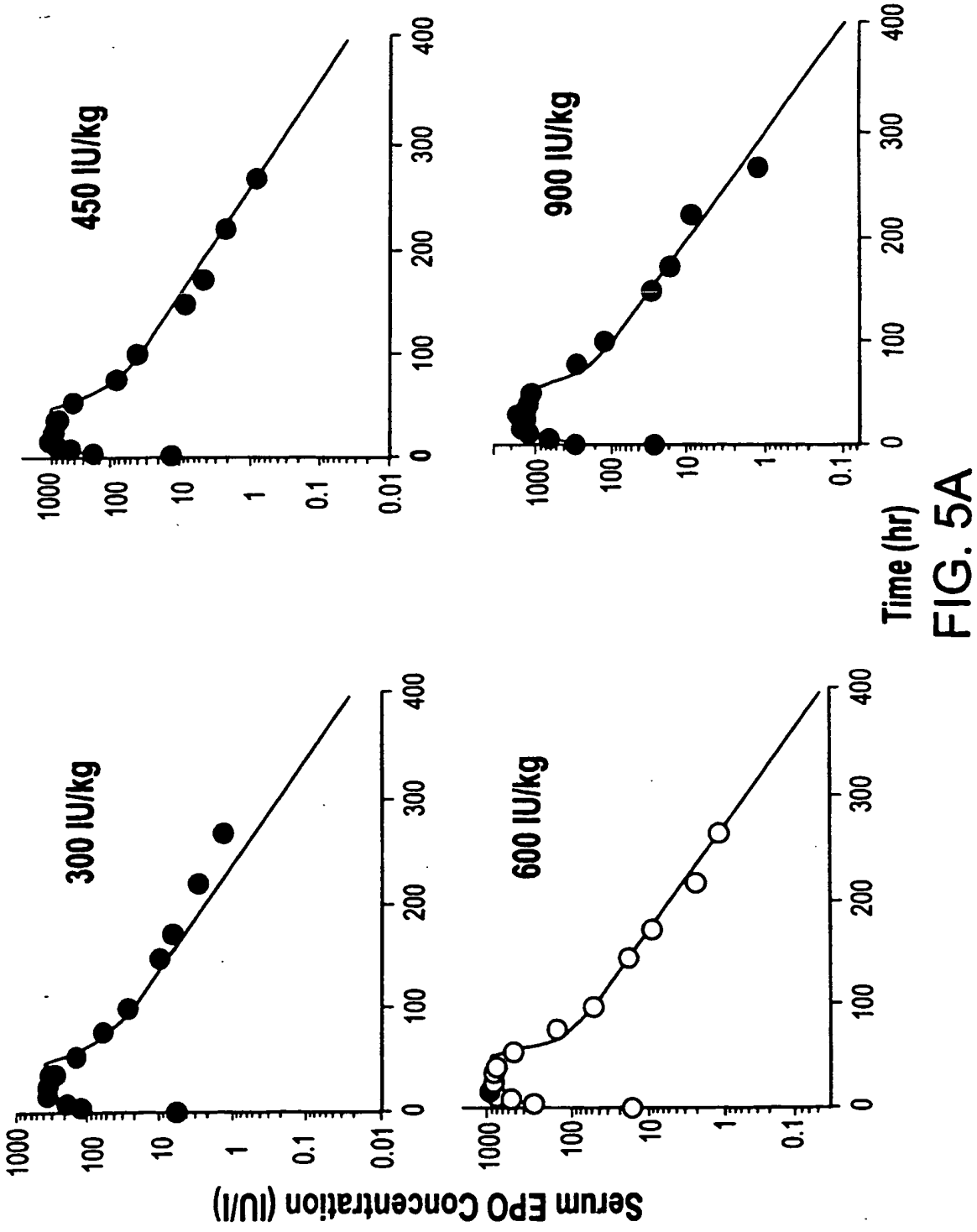

450 IU/kg
900 IU/kg
300 IU/kg
600 IU/kg
Serum EPO Concentration (IU/l)
Time (hr)
1000
100
10
1
0.1
0.01
0
100
200
300
400

FIG. 5A

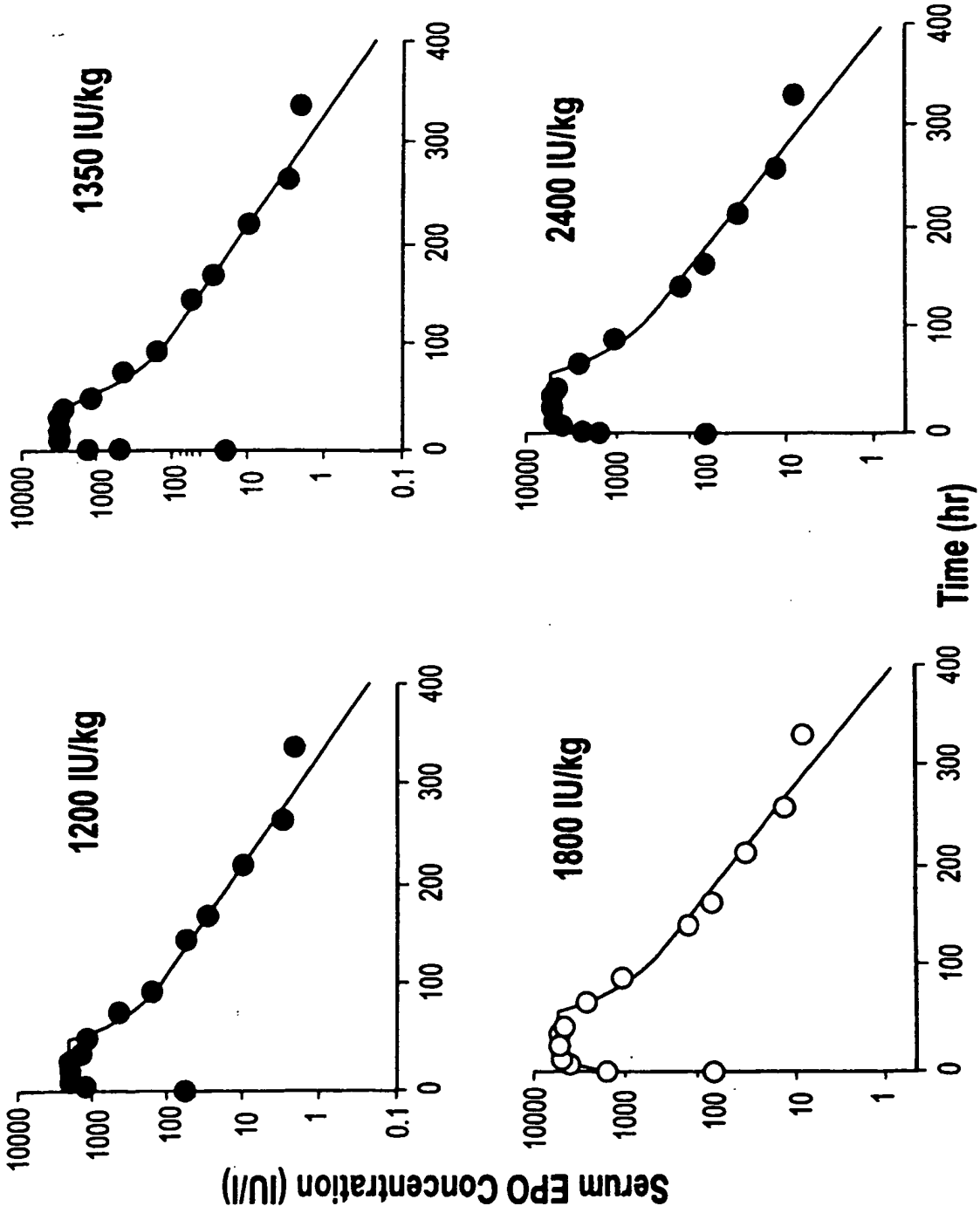

1350 IU/kg
2400 IU/kg
1200 IU/kg
1800 IU/kg
Serum EPO Concentration (IU/l)
Time (hr)
10000
1000
100
10
1
0.1
0
100
200
300
400

FIG. 5B

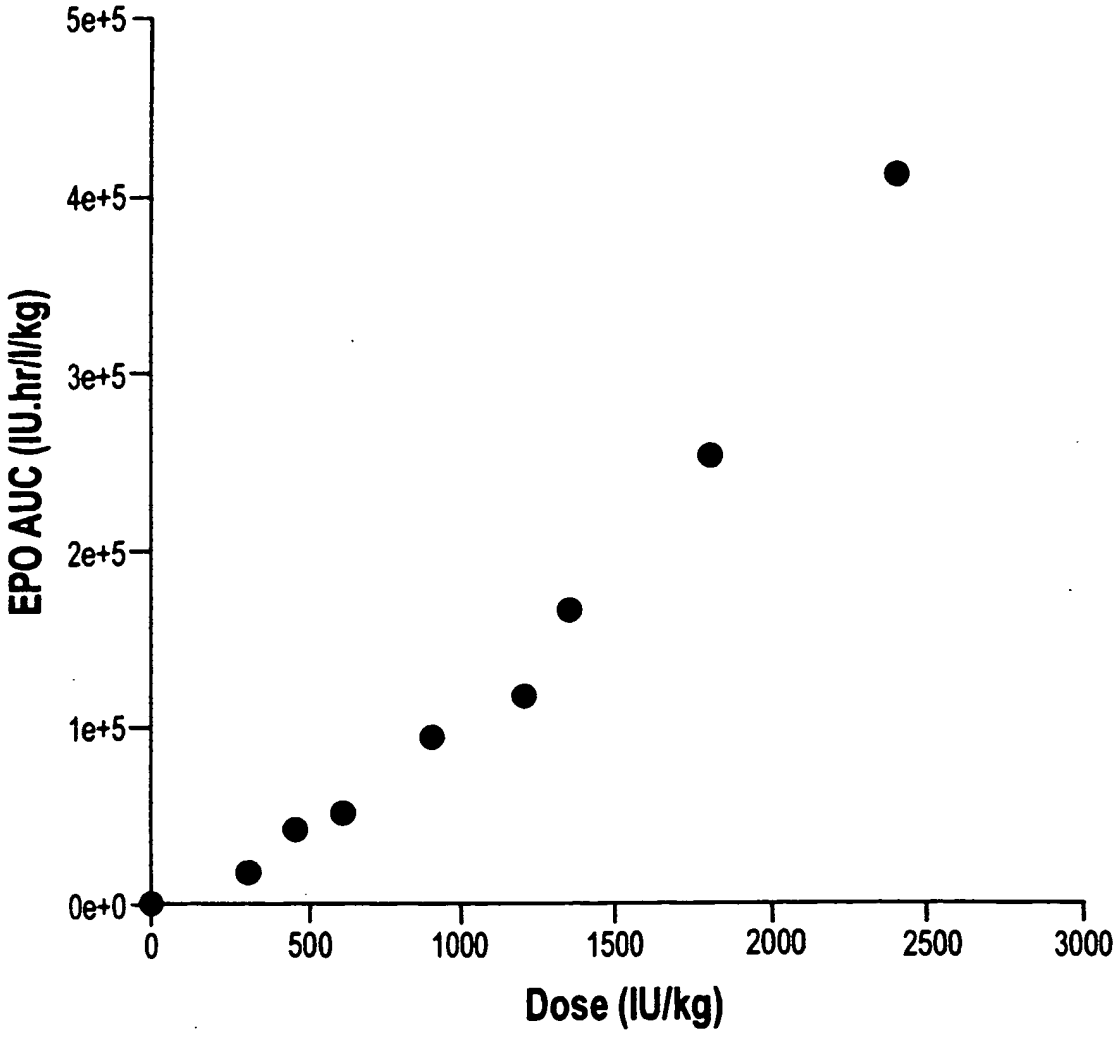

5e+5
4e+5
3e+5
2e+5
1e+5
0e+0
EPO AUC (IU.hr/l/kg)
0
500
1000
1500
2000
2500
3000
Dose (IU/kg)

FIG. 6

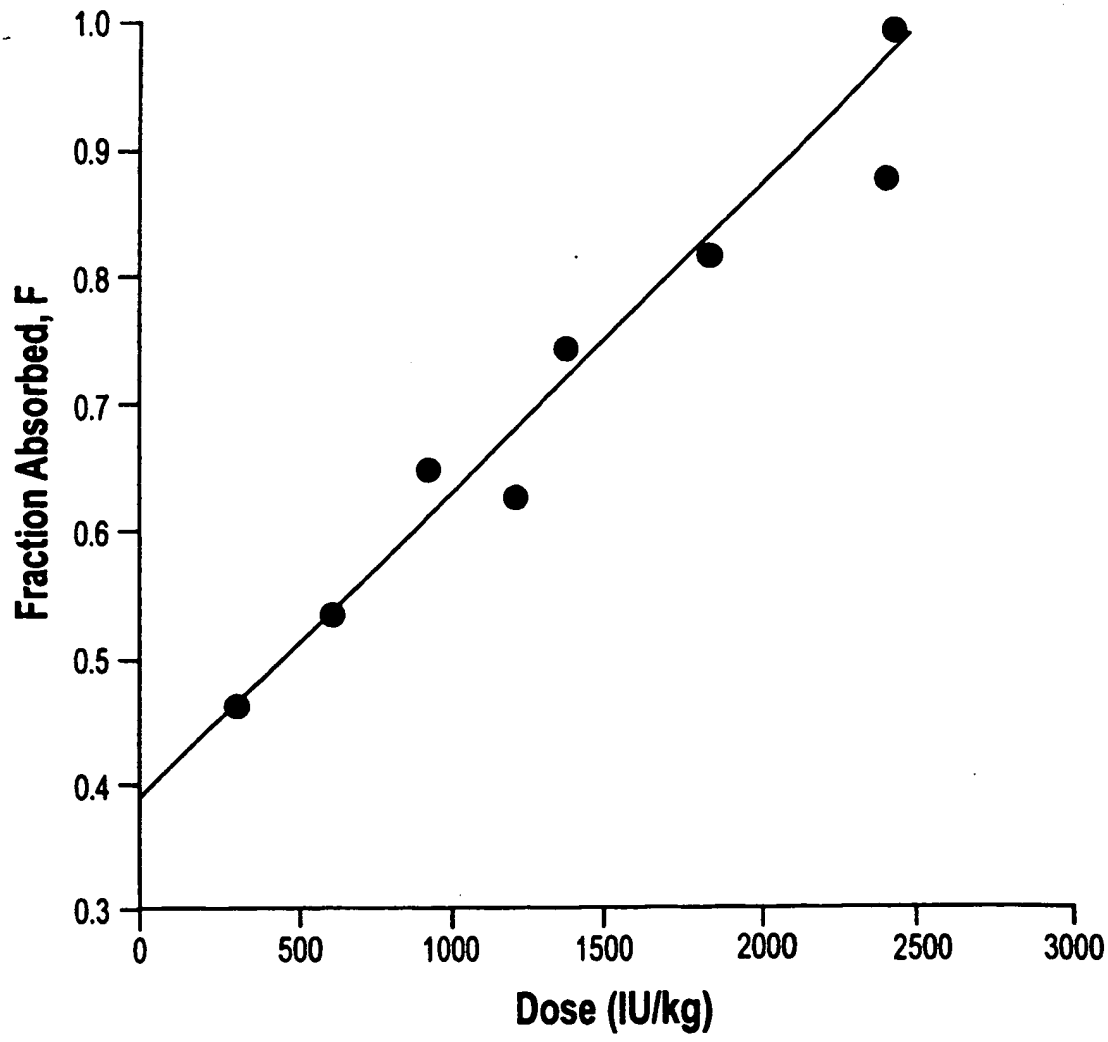

Fraction Absorbed, F
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0
500
1000
1500
2000
2500
3000
Dose (IU/kg)

FIG. 7

## BIOAVAILABILITY VALUES FOR SUBCUTANEOUS EPO

| DOSE (IU/kg) | F (fitted) | F (linear regression) | F (deconvolution) |
|---|---|---|---|
| 300 | 0.464 | 0.463 | 0.36 |
| 450 | 0.614 | 0.50 | 0.56 |
| 600 | 0.535 | 0.538 | 0.51 |
| 900 | 0.651 | 0.613 | 0.61 |
| 1200 | 0.631 | 0.688 | 0.57 |
| 1350 | 0.748 | 0.752 | 0.73 |
| 1800 | 0.823 | 0.836 | 0.83 |
| 2400 | 1.00 | 0.987 | 1.00 |

FIG. 8

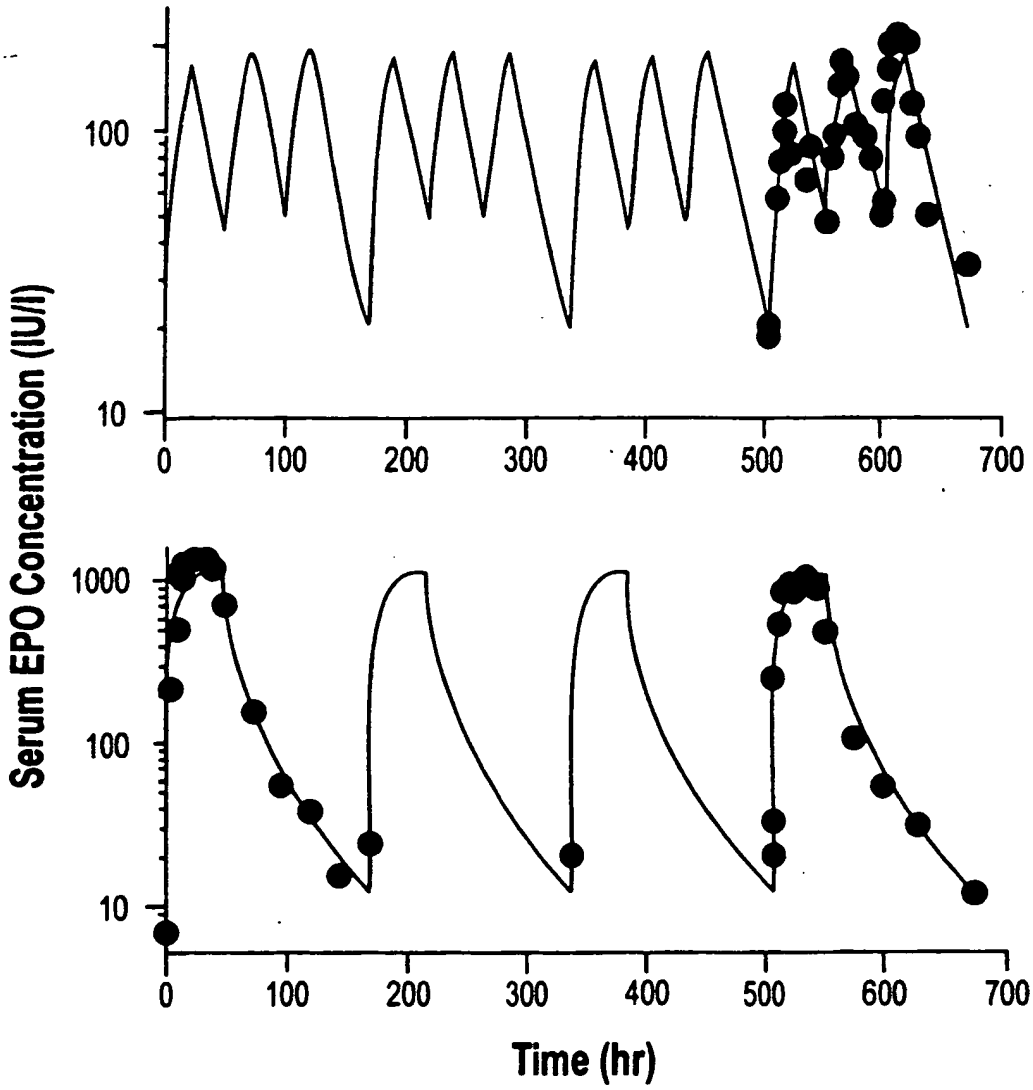

Serum EPO Concentration (IU/l)
100
10
0
100
200
300
400
500
600
700
1000
100
10
0
100
200
300
400
500
600
700
Time (hr)

FIG. 9

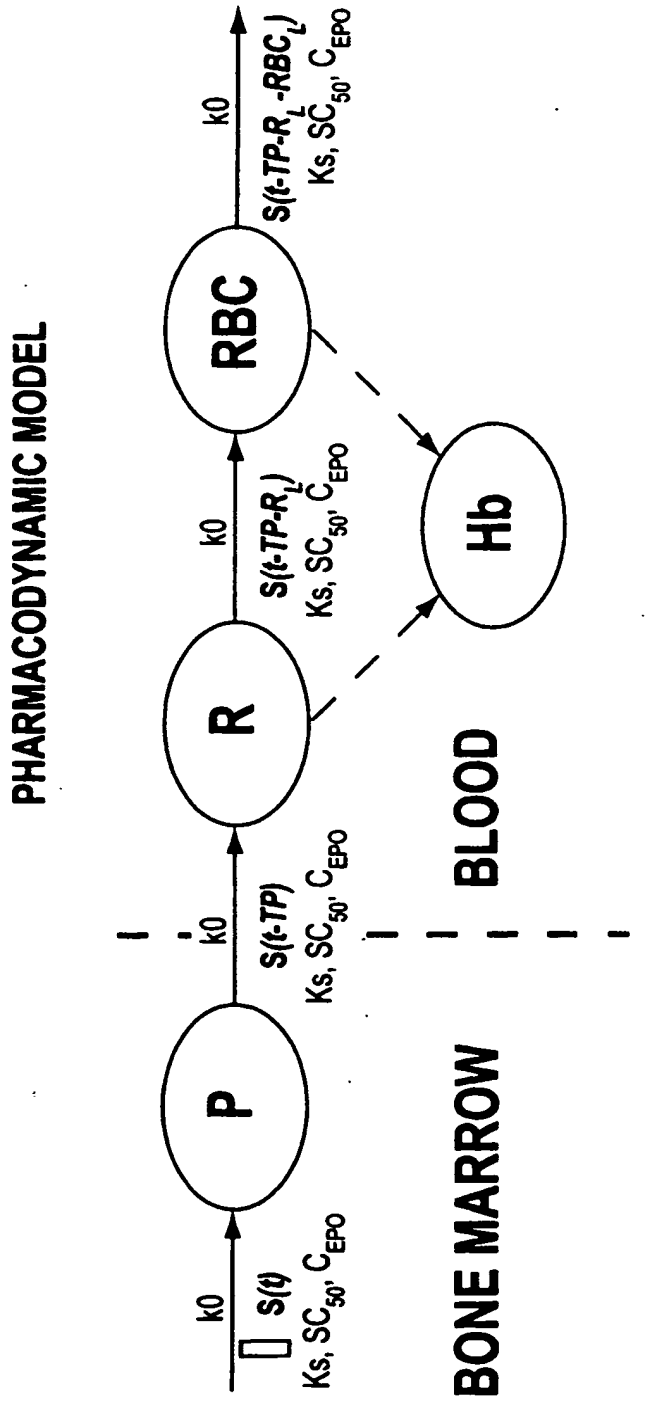

PHARMACODYNAMIC MODEL
BONE MARROW
BLOOD
P
R
RBC
Hb
k0
k0
k0
k0
S(t)
Ks, SC50, CEPO
S(t-TP)
Ks, SC50, CEPO
S(t-TP-RL)
Ks, SC50, CEPO
S(t-TP-RL-RBCL)
Ks, SC50, CEPO

FIG. 10

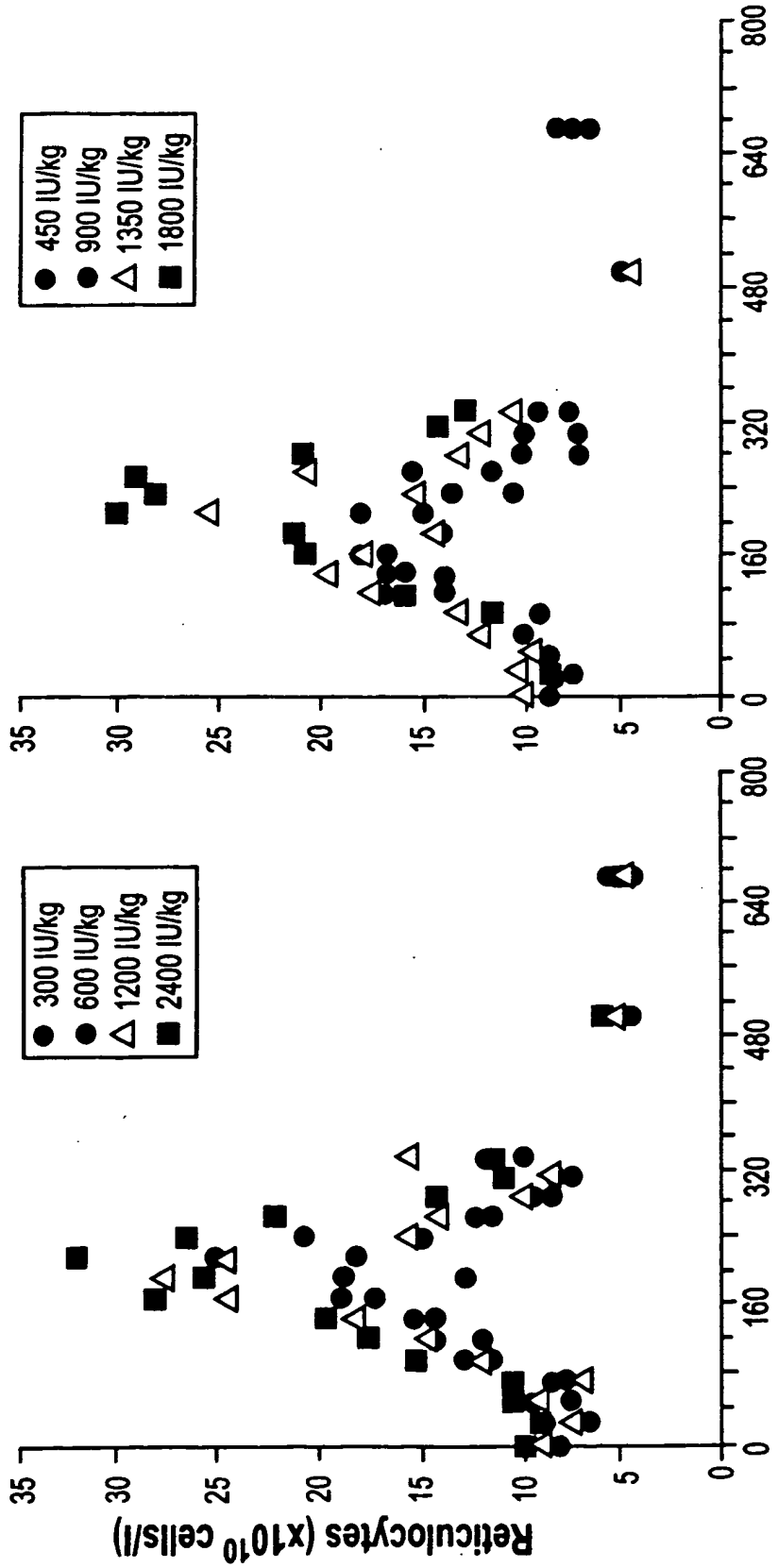

Reticulocytes (x10^10 cells/l)
Time (hr)
300 IU/kg
600 IU/kg
1200 IU/kg
2400 IU/kg
450 IU/kg
900 IU/kg
1350 IU/kg
1800 IU/kg
0
5
10
15
20
25
30
35
160
320
480
640
800

FIG. 11

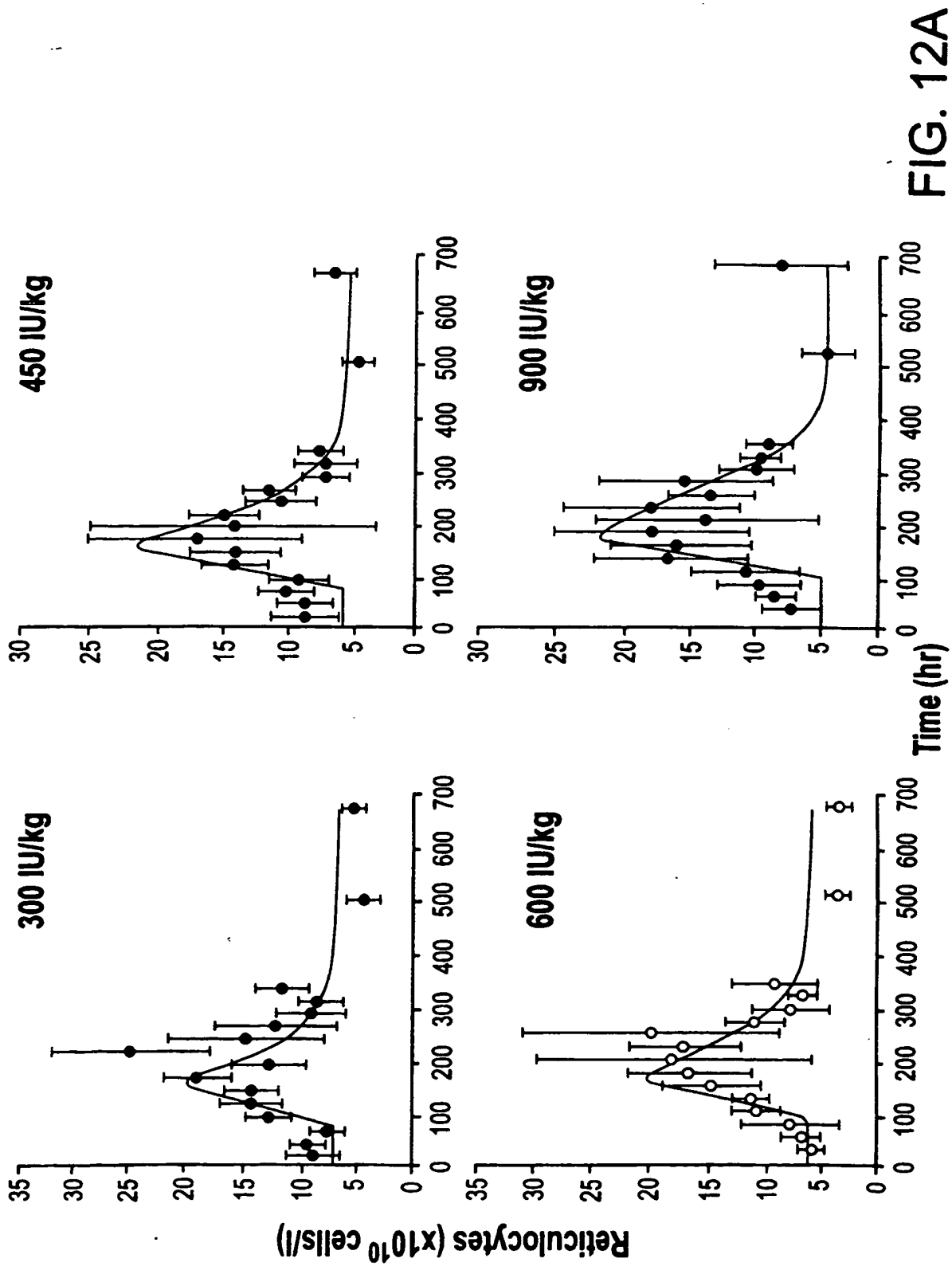

450 IU/kg
900 IU/kg
300 IU/kg
600 IU/kg
Reticulocytes (x10^10 cells/l)
Time (hr)

FIG. 12A

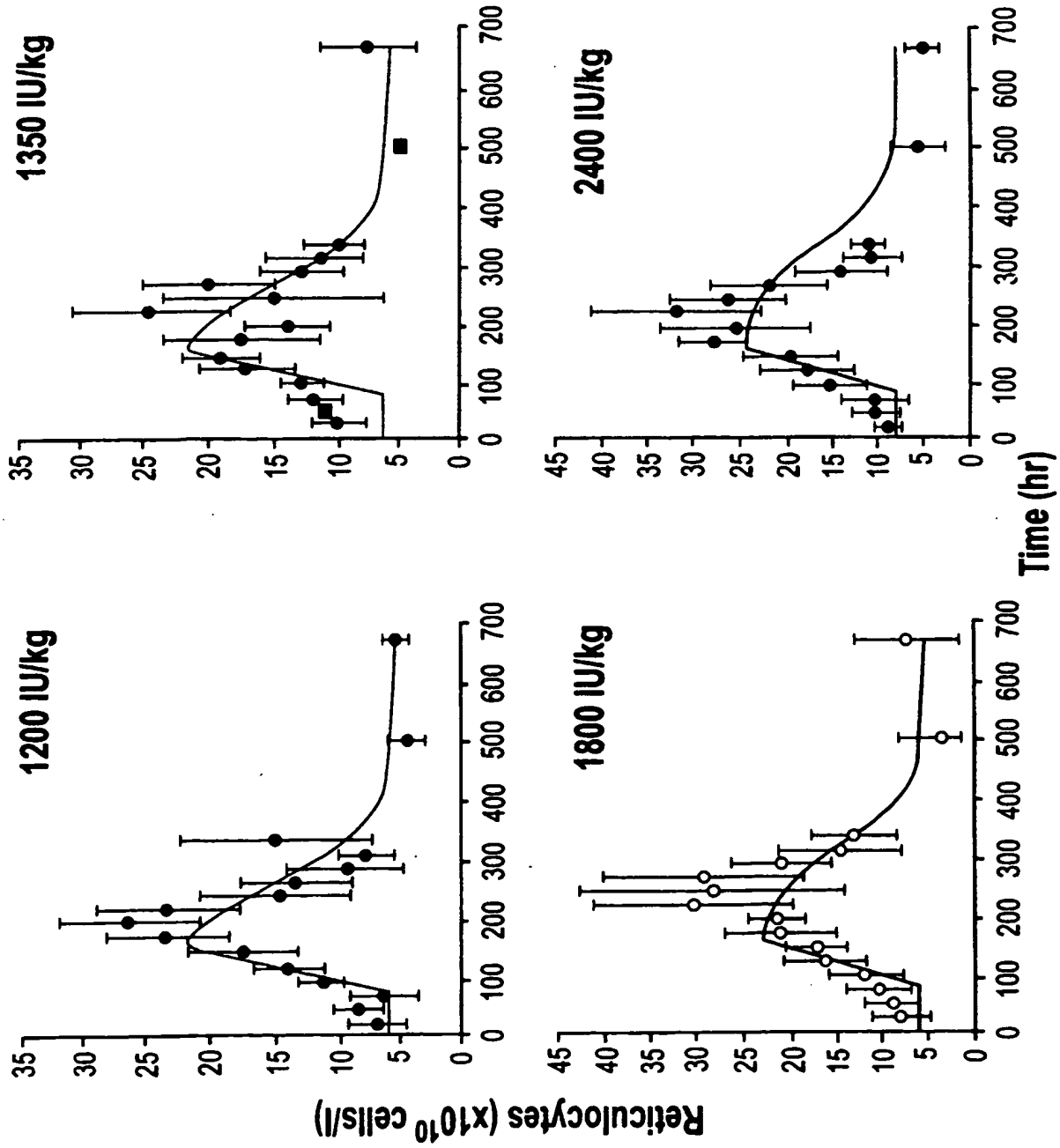

1350 IU/kg
2400 IU/kg
1200 IU/kg
1800 IU/kg
Reticulocytes (x10^10 cells/l)
Time (hr)
0
100
200
300
400
500
600
700
5
10
15
20
25
30
35
40
45

FIG. 12B

## PHARMACODYNAMIC PARAMETERS FOR SUBCUTANEOUS EPO EFFECTS

| | PARAMETER | ESTIMATE |
|---|---|---|
| **ESTIMATED:** | Ks (cells/l/hr) | $0.3709 \times 10^{10}$ |
| | SC50 (IU/l) | 22.58 |
| | TP (hr) | 81.96 |
| **FIXED:** | | |
| | $R_L$ (hr) | 72 |
| | $RCB_L$ (hr) | 2880 |
| | Hb (pg/cell) | 29.5 |
| | Threshold (=SC50; IU/l) | 22.58 |

FIG.13

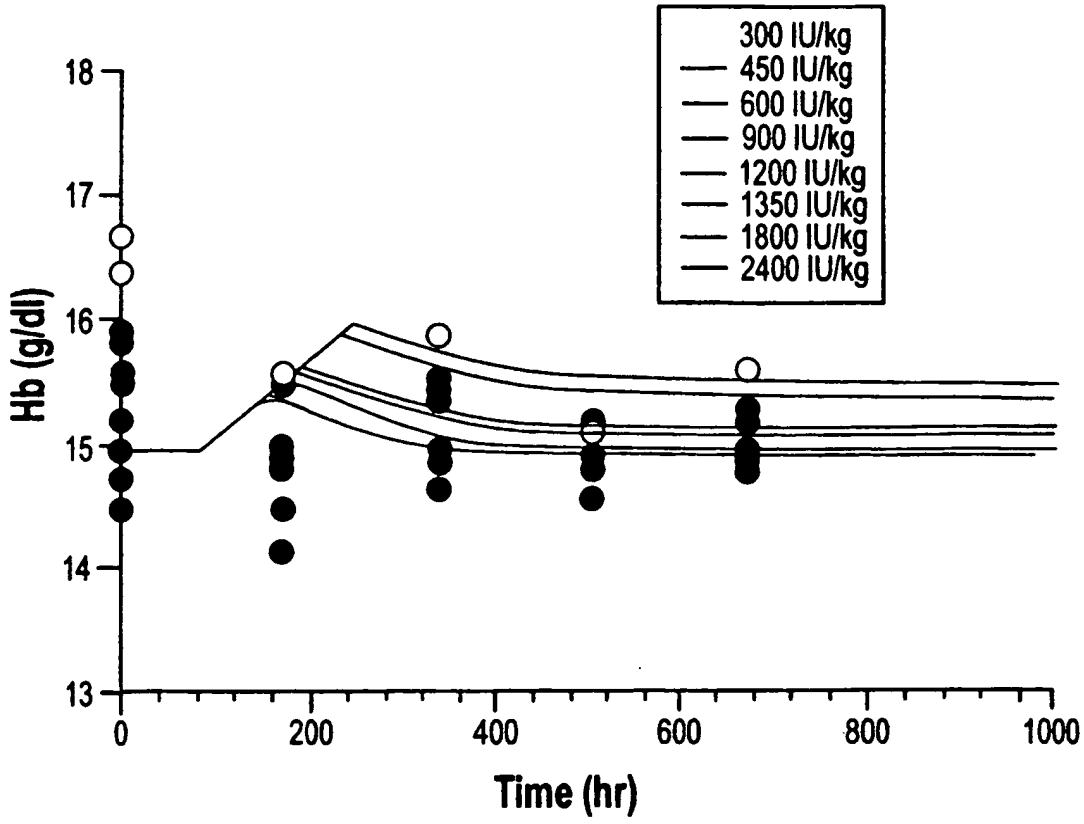

300 IU/kg
450 IU/kg
600 IU/kg
900 IU/kg
1200 IU/kg
1350 IU/kg
1800 IU/kg
2400 IU/kg
Hb (g/dl)
18
17
16
15
14
13
0
200
400
600
800
1000
Time (hr)

FIG. 14

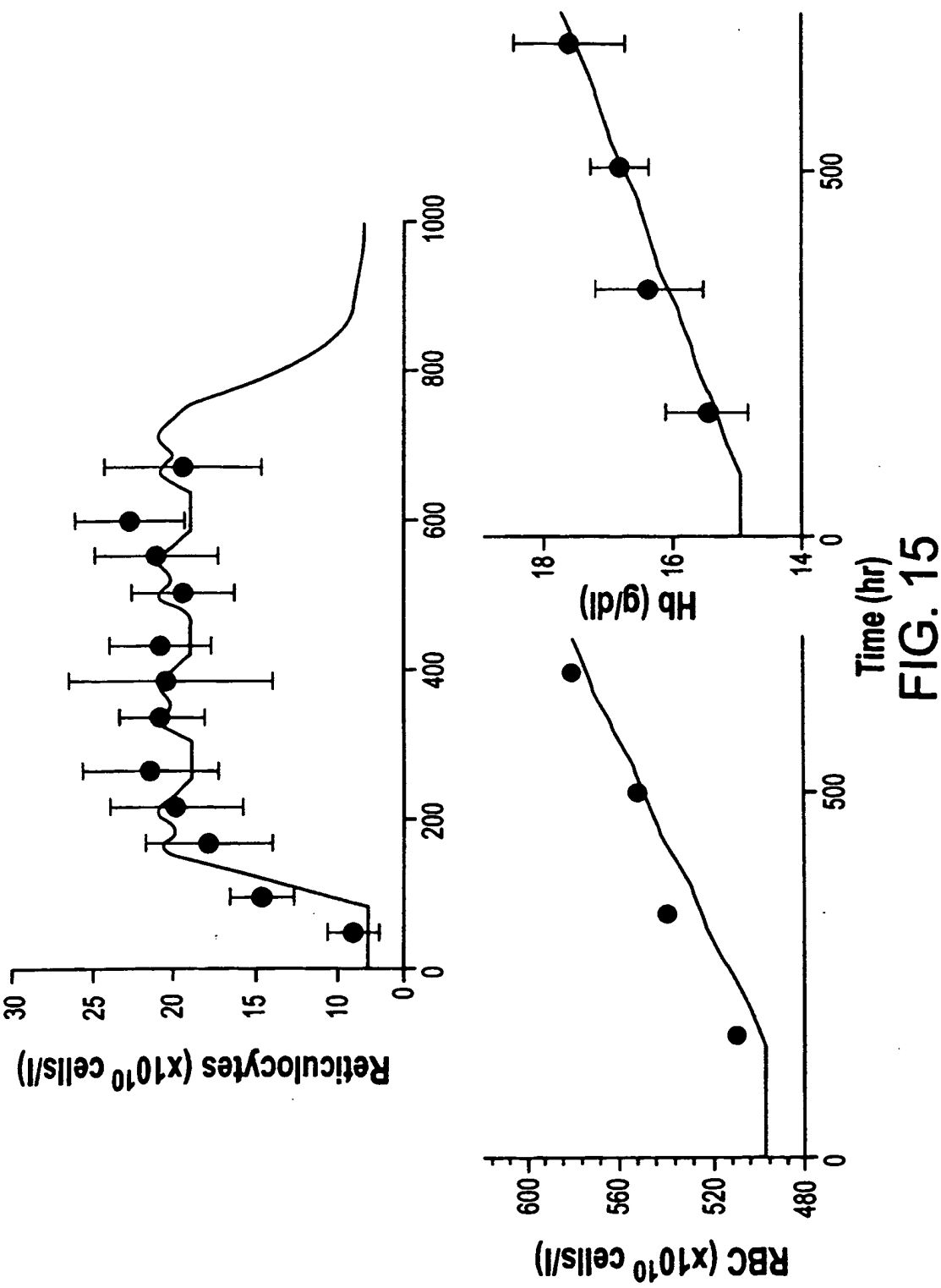

Reticulocytes (x10^10 cells/l)
0
10
15
20
25
30
0
200
400
600
800
1000
Hb (g/dl)
14
16
18
0
500
RBC (x10^10 cells/l)
480
520
560
600
0
500
Time (hr)

FIG. 15

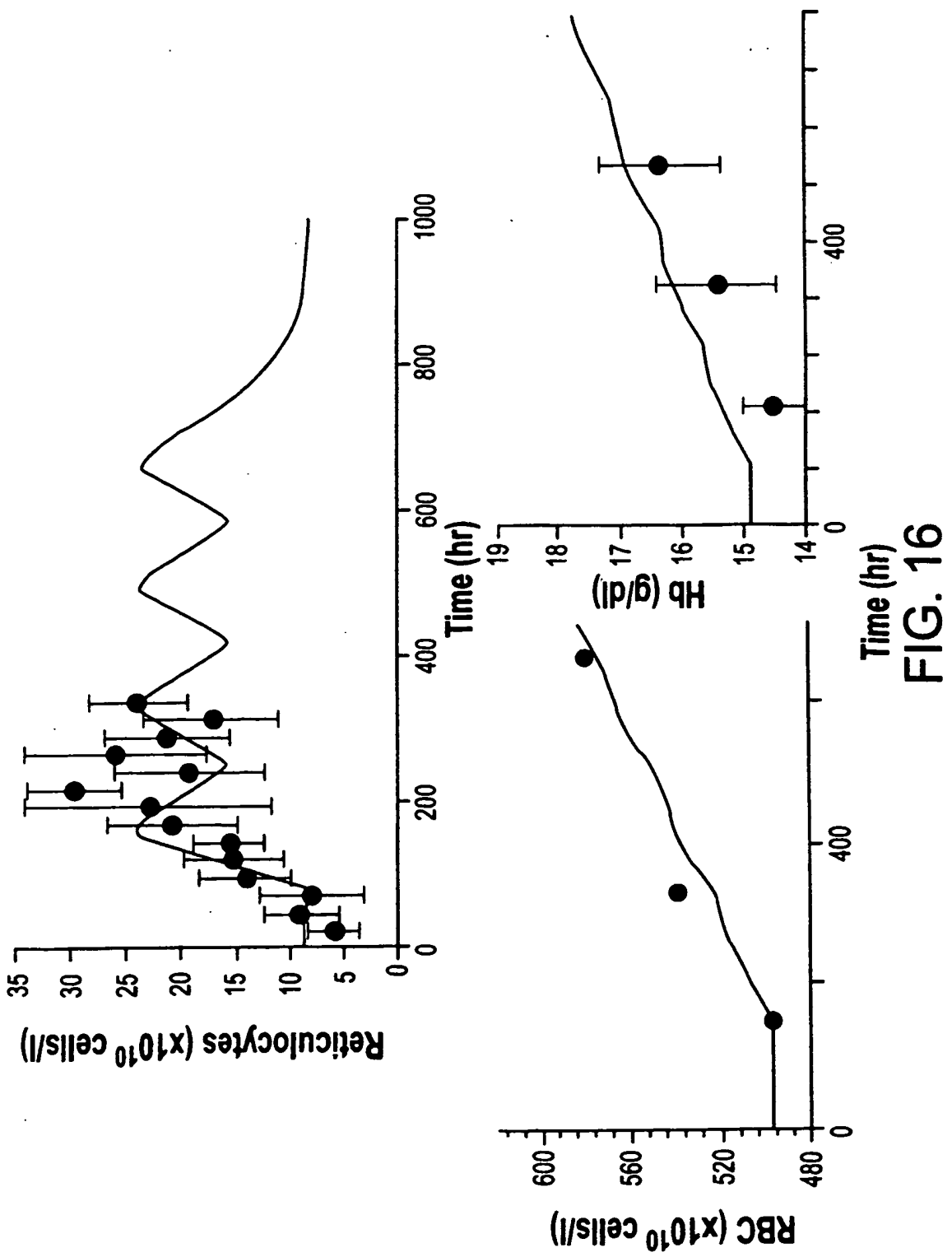

Reticulocytes (x10^10 cells/l)
0
5
10
15
20
25
30
35
0
200
400
600
800
1000
Time (hr)
Hb (g/dl)
14
15
16
17
18
19
0
400
Time (hr)
RBC (x10^10 cells/l)
480
520
560
600
0
400

FIG. 16

| Study Type/Description | Study Identifier | Ref No. |
|---|---|---|
| Pharmacokinetics/Pharmacodynamics<br>Single-center, open-label, parallel design, randomized study conducted in 36 healthy subjects (36 enrolled and analyzed for safety; 34 completed and analyzed for pharmacokinetic and pharmacodynamic [PK/PD]). Subjects were randomized to two treatment groups and received Epoetin alfa as either the standard cancer regimen (150 IU/kg s.c. t.i.w.) or a weekly fixed dose regimen (40,000 IU s.c. q.w.) for 4 wk. | EPO-PHI-373<br>(Pivotal) | 1 |
| Pharmacokinetics/Pharmacodynamics<br>Single-center, open-label, parallel design, randomized study conducted in 49 healthy subjects (49 enrolled and analyzed for safety; 46 completed and analyzed for PK/PD). Subjects were randomized to two treatment groups and received Epoetin alfa as either the standard cancer regimen (150 IU/kg s.c. t.i.w.) or a weekly fixed dose regimen (40,000 IU s.c. q.w.) for 4 wk. | EPO-PHI-370<br>(Supportive) | 2 |
| Pharmacokinetics/Pharmacodynamics<br>Open-label, randomized, placebo controlled, parallel-group, single-center study conducted in 32 subjects (32 enrolled and analyzed for safety; 30 completed and analyzed for PK/PD). Subjects were randomized into three treatment groups (N = 5 each) to receive one of the six treatments (450-, 900-, 1350-, and 1800-IU/kg single s.c. dose, and 150-IU/kg s.c. t.i.w. for 4 wk). | EPO-PHI-358<br>(Pilot exploratory) | 3 |
| Pharmacokinetics/Pharmacodynamics<br>Open-label, randomized, placebo controlled, parallel-group, single-center study conducted in 30 subjects. Subjects were randomized into six treatment groups (N = 5 each) to receive one of the six treatments (300-, 600-, 1200-, and 2400-IU/kg single s.c. dose, and 600-IU/kg s.c. q.w. for 4 wk). | EPO-PHI-359<br>(Pilot exploratory) | 4 |

FIG. 17

| Applicant: | The R.W. Johnson Pharmaceutical Research Institute |
|---|---|
| Drug: | Epoetin Alfa Once Weekly Dosing |
| NDA No.: | Insert NDA No. |

| Study No (Ref No.) | Study Type | Dosage Form(s) Study Design | Dose | Batch No. Plant/Date Manufactured | No. of Subjects | Related IND or NDA No.s. | Submission Date | Applicant Conclusion | Previous Agency Responses on Study with Date of Correspondence |
|---|---|---|---|---|---|---|---|---|---|
| RWJPRI Clinical Study EPO-PHI-373 (1) | s.c. | 10,000 IU/ml solution for s.c. injection (Formula FD 22512-000-T-45)<br><br>40,000 IU/ml solution for s.c. injection (Formula FD 22512-000-AA-45)<br><br>Single-center, open-label, parallel-design, randomized study in healthy subjects. Two parallel treatment groups: 150 IU/kg s.c. t.i.w. x 4 wk and 40,000 IU q.w. x 4 wk. | 150 IU/kg t.i.w. s.c. administration for 4 wk<br><br>40,000 IU q.w. s.c. administration for 4 wk | 10,000 IU/ml formulation: 99KS077 Manufactured at Cilag AG Switzerland in Oct 1999<br><br>40,000 IU/ml formulation: 99KS091 Manufactured at Cilag AG< Switzerland in Oct 1999 | 36 enrolled 34 analyzed | NA | NA | Despite the difference in total exposure of erythropoietin in serum (AUC of Epoetin alfa) after the 150-IU/kg t.i.w. and the 40,000-IU q.w. dosing regimens, the hemoglobin responses to the two regimens were similar. | |

FIG. 18A

| Applicant: | The R.W. Johnson Pharmaceutical Research Institute |
|---|---|
| Drug: | Epoetin Alfa Once Weekly Dosing |
| NDA No.: | Insert NDA No. |

| Study No (Ref No.) | Study Type | Dosage Form(s) Study Design | Dose | Batch No. Plant/Date Manufactured | No. of Subjects | Related IND or NDA No.s | Submission Date | Applicant Conclusion | Previous Agency Responses on Study with Date of Correspondence |
|---|---|---|---|---|---|---|---|---|---|
| RWJPRI Clinical Study EPO-PHI-370 (2) | s.c. | 10,000 IU/ml solution for s.c. injection (Formula FD 22512-000-C-45)<br><br>40,000 IU/ml solution for s.c. injection (Formula FD 22512-000-AC-45)<br><br>Single-center, open-label, parallel-design, randomized study in healthy subjects. Two parallel treatment groups: 150 IU/kg s.c. t.i.w. x 4 wk and 40,000 IU q.w. x 4 wk. | 150 IU/kg t.i.w. s.c. administration for 4 wk<br><br>40,000 IU q.w. s.c. administration for 4 wk | 10,000 UI/ml formulation: Lot D000123 Manufactured at Amgen Inc., Thousand Oaks, CA<br><br>40,000 IU/ml formulation: Lot D000175 Manufactured at Amgen Inc., Thousand Oaks, CA | 49 enrolled 46 analyzed | IND BB-IND-2318 | Protocol 01 Jul 1999<br><br>Ammended Protocols | Despite the difference in total exposure of erythropoietin in serum (AUC of Epoetin alfa) after the 150-IU/kg t.i.w. and the 40,000-IU q.w. dosing regimens, the hemoglobin responses to the two regimens were similar. | |

FIG. 18B

| Applicant: | The R.W. Johnson Pharmaceutical Research Institute |
|---|---|
| Drug: | Epoetin Alfa Once Weekly Dosing |
| NDA No.: | Insert NDA No. |

| Study No (Ref No.) | Study Type | Dosage Form(s) Study Design | Dose | Batch No. Plant/Date Manufactured | No. of Subjects | Related IND or NDA No.s | Submission Date | Applicant Conclusion | Previous Agency Responses on Study with Date of Correspondence |
|---|---|---|---|---|---|---|---|---|---|
| RWJPRI Clinical Study EPO-PHI-358 (3) | s.c. | 40,000 IU/ml solution for s.c. administration (Formula FD 22512-000-J-45)<br><br>Open-label, randomized, placebo controlled, parallel-group, single center study conducted in 32 subjects (32 enrolled and analyzed for safety; 30 completed and analyzed for PK/PD). Subjects were randomized into six treatment | Single s.c. dose: 450, 900, 1350, 1800 IU/kg<br><br>Multiple s.c. dose: 150 IU/kg t.i.w. for 4 wk | 5C903J, Manufactured at Hoffman La-Roche, Basel Switzerland; March 1995 | 32 enrolled<br><br>30 analyzed | IND BB-IND-2318 | Protocol 06 May 1996<br><br>Amended Protocol 06 May 1996 | Pharmacological response to Epoetin alfa is a function of dose and dosing regimen. The absorption rate of Epoetin alfa after subcutaneous administration was independent of dose. Clearance of Epoetin alfa was dose-dependent - it decreased with increasing dose. There was an increasing trend of AUC of reticulocytes with AUC of Epoetin alfa for single doses. A continuous pharmacological response (a continuous production of reticulocytes and sustained elevation of | |

FIG. 18C

| Applicant: | The R.W. Johnson Pharmaceutical Research Institute |
|---|---|
| Drug: | Epoetin Alfa Once Weekly Dosing |
| NDA No.: | Insert NDA No. |

| Study No (Ref No.) | Study Type | Dosage Form(s) Study Design | Dose | Batch No. Plant/Date Manufactured | No. of Subjects | Related IND or NDA No.s | Submission Date | Applicant Conclusion | Previous Agency Responses on Study with Date of Correspondence |
|---|---|---|---|---|---|---|---|---|---|
| | | groups (N = 5 each) to receive one of the six treatments (placebo 450, 900, 1350, and 1800 IU/kg single dose, and 150 IU/kg t.i.w. for 4 wk). | | | | | | hemoglobin) requires Epoetin alfa serum concentration to be maintained continuously (such as after 150 IU/kg t.i.w. dosing regimen) or intermittently (such as after the 600-IU/kg q.w. dosing regimen) above endogenous level. | |

FIG. 18C

| Applicant: | The R.W. Johnson Pharmaceutical Research Institute |
|---|---|
| Drug: | Epoetin Alfa Once Weekly Dosing |
| NDA No.: | Insert NDA No. |

| Study No (Ref No.) | Study Type | Dosage Form(s) Study Design | Dose | Batch No. Plant/Date Manufactured | No. of Subjects | Related IND or NDA No.s | Submission Date | Applicant Conclusion | Previous Agency Responses on Study with Date of Correspondence |
|---|---|---|---|---|---|---|---|---|---|
| RWJPRI Clinical Study EPO-PHI-359 (4) | s.c. | 40,000 IU/ml solution for s.c. administration (Formula FD 22512-000-J-45)<br><br>Open-label, randomized, placebo controlled, parallel-group, single center study conducted in healthy subjects. Subjects were randomized into six treatment groups (N = 5 each) to receive one of the six treatments (placebo 300, | Single s.c. dose: 300, 600, 1200, 2400 IU/kg<br><br>Multiple s.c. doses: 600 IU/kg q.w. for 4 wk | 5C903J, Manufactured at Hoffman La-Roche, Basel Switzerland; March 1995 | 30 enrolled<br><br>30 analyzed | IND BB-IND-2318 | 06 May 1996 | Pharmacological response to Epoetin alfa is a function of dose and dosing regimen. The absorption rate of Epoetin alfa after subcutaneous administration was independent of dose. Clearance of Epoetin alfa was dose-dependent - it decreased with increasing dose. There was an increasing trend of AUC of reticulocytes with AUC of Epoetin alfa for single doses. A continuous pharmacological response (a continuous production of reticulocytes and sustained elevation of | |

FIG. 18D

| Applicant: | The R.W. Johnson Pharmaceutical Research Institute |
|---|---|
| Drug: | Epoetin Alfa Once Weekly Dosing |
| NDA No.: | Insert NDA No. |

| Study No (Ref No.) | Study Type | Dosage Form(s) Study Design | Dose | Batch No. Plant/Date Manufactured | No. of Subjects | Related IND or NDA No.s | Submission Date | Applicant Conclusion | Previous Agency Responses on Study with Date of Correspondence |
|---|---|---|---|---|---|---|---|---|---|
| | | 600, 1200, 2400 IU/kg and 600 IU/kg q.w. for 4 wk). | | | | | | hemoglobin) requires Epoetin alfa serum concentration to be maintained continuously (such as after 150 IU/kg t.i.w. dosing regimen) or intermittently (such as after the 600-IU/kg q.w. dosing regimen) above endogenous level. | |

FIG. 18D

| Applicant: | The R.W. Johnson Pharmaceutical Research Institute | | | | | |
|---|---|---|---|---|---|---|
| Drug: | Epoetin Alfa Once Weekly Dosing | | | | | |
| NDA No.: | Insert NDA No. | | | | | |
| Study | Dose | $C_{max}$ (mIU/mL) | $t_{max}$ (h) | AUC[a] (mIU·h/mL) | CL/F (mL/h/kg) | $t_{1/2}$ (h) |
| Single Subcutaneous Dose Administration | | | | | | |
| EPO359 | 300 IU/kg | 429 ± 86 (20.0%) | 22.8 ± 8.1 (36.5%) | 20056 ± 4138 (20.6%) | 15.5 ± 3.1 (20.2%) | 68.2 ± 52.2 (76.6%) |
| EPO358 | 450 IU/kg | 1263 ± 290 (23.0%) | 15.6 ± 5.8 (37.0%) | 45498 ± 12342 (27.1%) | 10.4 ± 2.6 (24.9%) | 24.2 ± 3.2 (13.2%) |
| EPO359 | 600 IU/kg | 1263 ± 486 (38.5%) | 27.6 ± 9.1 (33.0%) | 55475 ± 16384 (29.5%) | 11.8 ± 4.2 (35.5%) | 29.3 ± 9.4 (32.0%) |
| EPO358 | 900 IU/kg | 2235 ± 599 (26.8%) | 22.2 ± 12.7 (57.0%) | 103154 ± 28024 (27.2%) | 9.36 ± 2.97 (31.7%) | 36.0 ± 13.5 (37.3%) |
| EPO359 | 1200 IU/kg | 2256 ± 710 (31.4%) | 26.4 ± 7.8 (29.4%) | 119932 ± 44217 (36.9%) | 11.2 ± 4.2 (37.7%) | 78.5 ± 95.4 (122%) |
| EPO358 | 1350 IU/kg | 3755 ± 879 (23.4%) | 23.4 ± 8.8 (37.8%) | 174193 ± 41417 (23.8%) | 8.23 ± 2.57 (31.3%) | 33.4 ± 2.4 (7.2%) |
| EPO358 | 1800 IU/kg | 4370 ± 1673 (38.3%) | 28.8 ± 7.8 (27.2%) | 258600 ± 101175 (39.1%) | 7.64 ± 2.22 (29.1%) | 32.4 ± 8.4 (25.9%) |
| EPO359 | 2400 IU/kg | 6819 ± 764 (11.2%) | 25.2 ± 6.2 (24.7%) | 429441 ± 32139 (7.5%) | 5.61 ± 0.44 (7.8%) | 43.6 ± 25.9 (59.5%) |
| Multiple Subcutaneous Dose Administration | | | | | | |
| EPO358 Wk 4 | 150 IU/kg t.i.w. | 252 ± 71 (28.0%) | NA | 16582 ± 4256 (25.7%) | 28.7 ± 7.8 (27.1%) | 25.9 ± 7.1 (27.2%) |
| EPO359 Wk 1 | 600 IU/kg q.w. | 1502 ± 384 (25.6%) | 21.6 ± 6.1 (28.5%) | 63439 ± 10893 (17.2%) | 9.70 ± 1.8 (18.1%) | 28.3 ± 7.5 (26.3%) |
| EPO359 Wk 4 | 600 IU/kg q.w. | 1278 ± 213 (16.6%) | 24.0 ± 8.7 (36.4%) | 50725 ± 6774 (13.4%) | 12.0 ± 1.6 (13.2%) | 28.1 ± 7.0 (24.9%) |

FIG. 19

| Applicant: | The R.W. Johnson Pharmaceutical Research Institute | | | | | |
|---|---|---|---|---|---|---|
| Drug: | Epoetin Alfa Once Weekly Dosing | | | | | |
| NDA No.: | Insert NDA No. | | | | | |
| Study | Dose | $C_{max}$ (mIU/mL) | $t_{max}$ (h) | AUC[a] (mIU·h/mL) | CL/F (mL/h/kg) | $t_{1/2}$ (h) |
| | | Single Subcutaneous Dose Administration | | | | |
| EPO370 Wk 4 | 150 IU/kg t.i.w. | 191 ± 100 (52.3%) | NA | 13446 ± 4374 (32.5%) | 37.1 ± 12.3 (33.1%) | 31.8 ± 13.4 (42.1%) |
| EPO370 Wk 4 | 40,000 IU q.w. | 785 ± 427 (54.4%0) | 18 ± 5 (29.4%) | 30084 ± 13516 (44.9%) | 23.2 ± 10.8 (46.5%) | 39.3 ± 7.1 (18.1%) |
| EPO373 Wk 4 | 150 IU/kg t.i.w. | 143 ± 54 (37.8%) | NA | 8587 ± 1521 (17.7%) | 54.1 ± 10.1 (18.7%) | 19.4 ± 8.1 (41.5%) |
| EPO373 Wk 4 | 40,000 IU q.w. | 861 ± 445 (51.7%) | 16 ± 8 (45.6%) | 25747 ± 9062 (35.2%) | 24.7 ± 7.2 (29.1%) | 15.0 ± 6.1 (40.9%) |

[a] AUC(0-168h) during a dose week for multiple dose regimens and AUC(0-672h) during the 4-wk of study period for single doses.

NA = Not applicable

FIG. 19

| Applicant: | The R.W. Johnson Pharmaceutical Research Institute | | | |
|---|---|---|---|---|
| Drug: | Epoetin Alfa Once Weekly Dosing | | | |
| NDA No.: | Insert NDA No. | | | |
| Study No. Primary Supportive (Ref. No.) | Type of Biological Fluid | Analysis Method | Sensitivity of Method Range (mU/mL) | Specificity of Assay |
| EPO-PHI-358 Pilot /Exploratory | Serum | RIA (RWJPRI)[23] | 7.8-125 | Detects both endogenous and exogenous EPO |
| EPO-PHI-359 Pilot /Exploratory | Serum | RIA (RWJPRI)[23] | 7.8-125 | Detects both endogenous and exogenous EPO |
| EPO-PHI-370 Supportive | Serum | RIA (PPD)[24] | 7.8-125 | Detects both endogenous and exogenous EPO |
| EPO-PHI-373 Pivotal | Serum | ELISA (PPD)[25] | 7.8-125 | Detects both endogenous and exogenous EPO |

FIG. 20

## Mean ± SD Demographic and Baseline Parameters for Subjects Enrolled in Clinical Studies EPO-PHI-358 and EPO-PHI-359

| Parameter | EPO-PHI-358 (N=32) | EPO-PHI-359 (N=30) |
|---|---|---|
| Age (yr) | 35.7 ± 7.25 | 34.1 ± 6.76 |
| Weight (kg) | 76.7 ± 7.10 | 77.7 ± 8.83 |
| Height (cm) | 174.2 ± 7.69 | 174.7 ± 7.88 |
| Race | | |
| White | 8 (25%) | 9 (30%) |
| Black | 4 (13%) | 1 (3%) |
| Asian | 0 (0%) | 1 (3%) |
| Hispanic | 20 (63%) | 19 (63%) |

FIG. 21

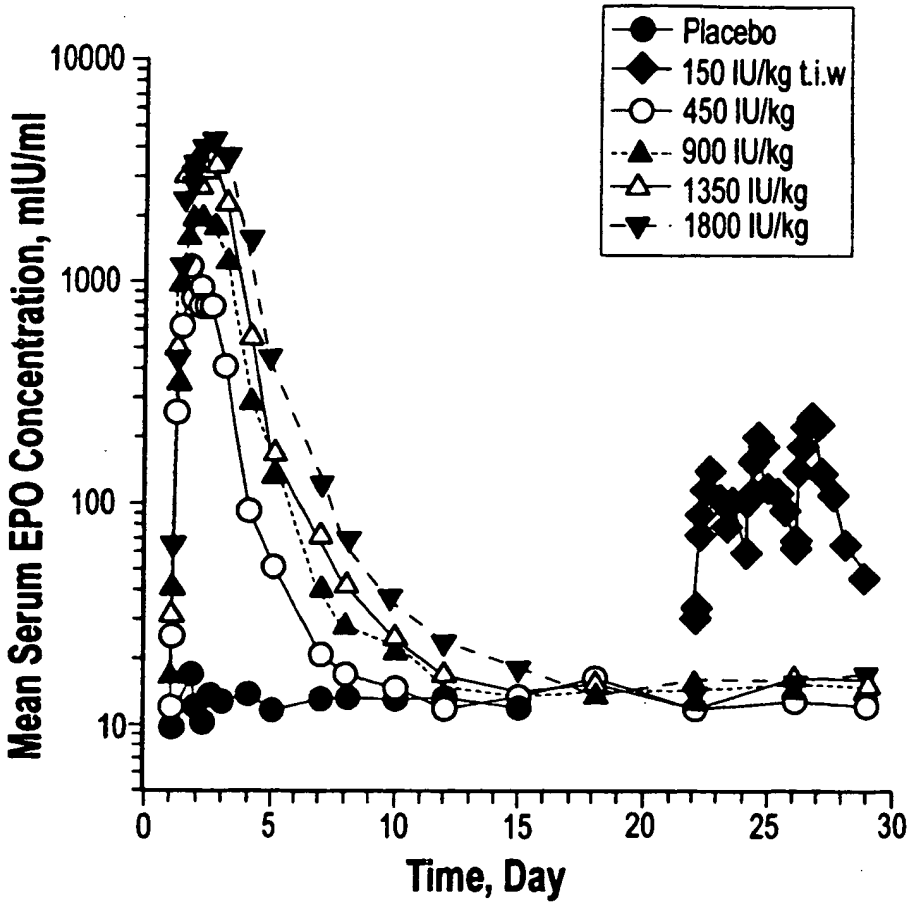

Placebo
150 IU/kg t.i.w
450 IU/kg
900 IU/kg
1350 IU/kg
1800 IU/kg
Mean Serum EPO Concentration, mIU/ml
10000
1000
100
10
0
5
10
15
20
25
30
Time, Day

FIG. 22

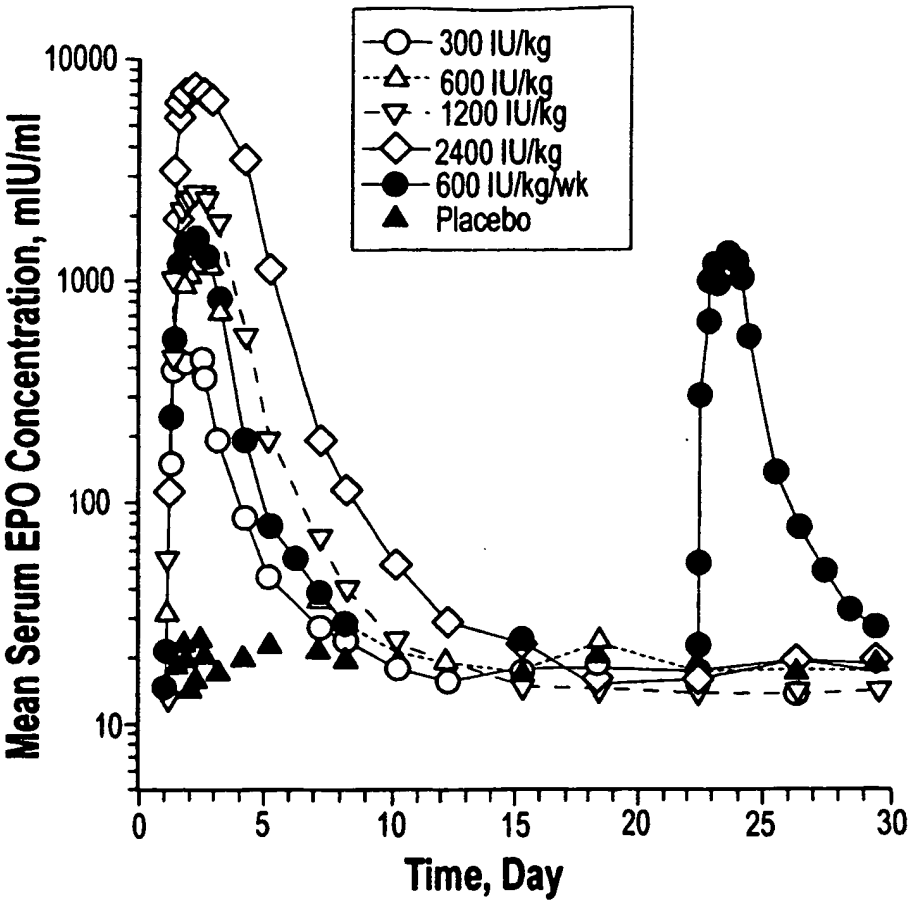

300 IU/kg
600 IU/kg
1200 IU/kg
2400 IU/kg
600 IU/kg/wk
Placebo
Mean Serum EPO Concentration, mIU/ml
10000
1000
100
10
0
5
10
15
20
25
30
Time, Day

FIG. 23

## Mean ± SD (%CV) Pharmacokinetic and Pharmacodynamic Parameters (Clinical Studies EPO-PHI-358 and EPO-PHI-359)

| Study | Dose | $C_{max}$ (mIU/mL) | $t_{max}$ (h) | AUC[a] (mIU·h/mL) | CL/F (mL/h/kg) | $t_{1/2}$ (h) | %RETI[b] AUC (%•h) |
|---|---|---|---|---|---|---|---|
| EPO359 | 300 IU/kg | 429 ± 86 (20.0%) | 22.2 ± 8.1 (36.5%) | 20056 ± 4138 (20.6%) | 15.5 ± 3.1 (20.2%) | 68.2 ± 52.2 (76.6%) | 1280 ± 157 (12.3%) |
| EPO358 | 450 IU/kg | 1263 ± 290 (23.0%) | 15.6 ± 5.8 (37.0%) | 45498 ± 12342 (27.1%) | 10.4 ± 2.6 (24.9%) | 24.2 ± 3.2 (13.2%) | 1191 ± 164 (13.8%) |
| EPO359 | 600 IU/kg | 1263 ± 486 (38.5%) | 27.6 ± 9.1 (33.0%) | 55475 ± 16384 (29.5%) | 11.8 ± 4.2 (35.5%) | 29.3 ± 9.4 (32.0%) | 1224 ± 227 (18.5%) |
| EPO358 | 900 IU/kg | 2235 ± 599 (26.8%) | 22.2 ± 12.7 (57.0%) | 103154 ± 28024 (27.2%) | 9.36 ± 2.97 (31.7%) | 36.0 ± 13.5 (37.3%) | 1296 ± 274 (21.1%) |
| EPO359 | 1200 IU/kg | 2256 ± 710 (31.4%) | 26.4 ± 7.8 (29.4%) | 119932 ± 44217 (36.9%) | 11.2 ± 4.2 (37.7%) | 78.5 ± 95.4 (122%) | 1413 ± 315 (22.3%) |
| EPO358 | 1350 IU/kg | 3755 ± 879 (23.4%) | 23.4 ± 8.8 (37.8%) | 174193 ± 41417 (23.8%) | 8.23 ± 2.57 (31.3%) | 33.4 ± 2.4 (7.2%) | 1406 ± 146 (10.4%) |
| EPO358 | 1800 IU/kg | 4370 ± 1673 (38.3%) | 28.8 ± 7.8 (27.2%) | 258600 ± 101175 (39.1%) | 7.64 ± 2.22 (29.1%) | 32.4 ± 8.4 (25.9%) | 1679 ± 407 (24.2%) |
| EPO359 | 2400 IU/kg | 6819 ± 764 (11.2%) | 25.2 ± 6.2 (24.7%) | 429441 ± 32139 (7.5%) | 5.61 ± 0.44 (7.8%) | 43.6 ± 25.9 (59.5%) | 1720 ± 233 (13.5%) |
| EPO358 Wk 4 | 150 IU/kg t.i.w. | 252 ± 71 (28.0%) | NA | 16582 ± 4256 (25.7%) | 28.7 ± 7.8 (27.1%) | 25.9 ± 7.1 (27.2%) | |

FIG. 24

**Mean ± SD (%CV) Pharmacokinetic and Pharmacodynamic Parameters (Clinical Studies EPO-PHI-358 and EPO-PHI-359)**

| Study | Dose | $C_{max}$ (mIU/mL) | $t_{max}$ (h) | AUC[a] (mIU·h/mL) | CL/F (mL/h/kg) | $t_{1/2}$ (h) | %RETI[b] AUC (%·h) |
|---|---|---|---|---|---|---|---|
| EPO358 Wk 1-4 | 150 IU/kg t.i.w. | | | | | | 1749 ± 406 (23.2%) |
| EPO359 Wk 1 | 600 IU/kg/wk | 1502 ± 384 (25.6%) | 21.6 ± 6.1 (28.5%) | 63439 ± 10893 (17.2%) | 9.70 ± 1.8 (18.1%) | 28.3 ± 7.5 (26.3%) | |
| EPO359 Wk 4 | 600 IU/kg/wk | 1278 ± 213 (16.6%) | 24.0 ± 8.7 (36.4%) | 50725 ± 6774 (13.4%) | 12.0 ±1.6 (13.2%) | 28.1 ± 7.0 (24.9%) | |
| EPO359 Wk 1-4 | 600 IU/kg/wk | | | | | | 2220 ± 493 (22.2%) |

[a] AUC(0-168) during a dosing week for multiple dose regimens and AUC(0-672) during the 4 wk of study period for single doses.

[b] Percent reticulocyte AUC from time-zero to Day 29 after initiation of drug administration.

NA = not applicable

FIG. 24

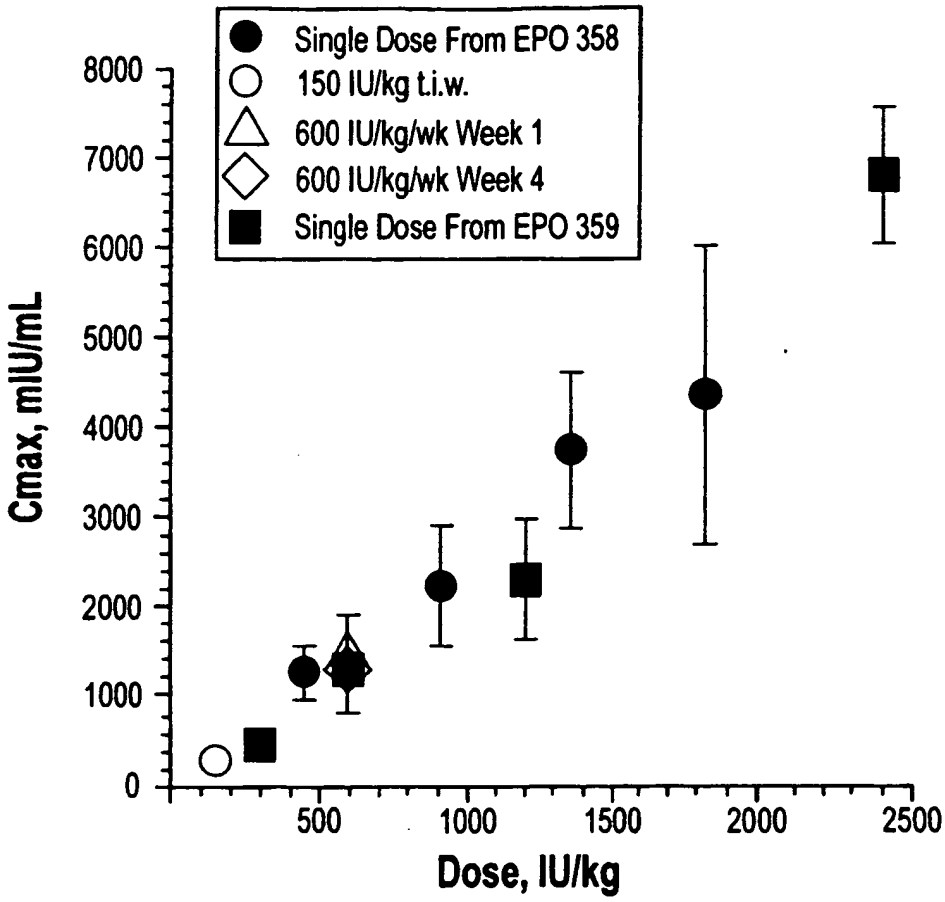

Single Dose From EPO 358
150 IU/kg t.i.w.
600 IU/kg/wk Week 1
600 IU/kg/wk Week 4
Single Dose From EPO 359
Cmax, mIU/mL
8000
7000
6000
5000
4000
3000
2000
1000
0
500
1000
1500
2000
2500
Dose, IU/kg

FIG. 25

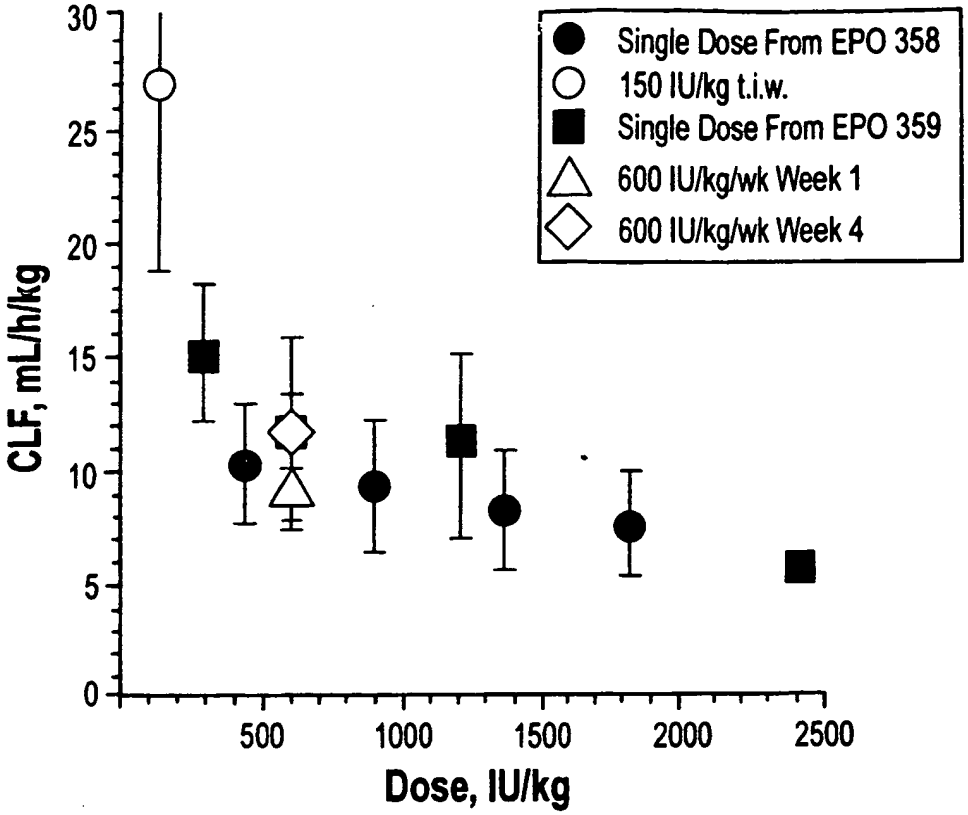

Single Dose From EPO 358
150 IU/kg t.i.w.
Single Dose From EPO 359
600 IU/kg/wk Week 1
600 IU/kg/wk Week 4
CLF, mL/h/kg
30
25
20
15
10
5
0
500
1000
1500
2000
2500
Dose, IU/kg

FIG. 26

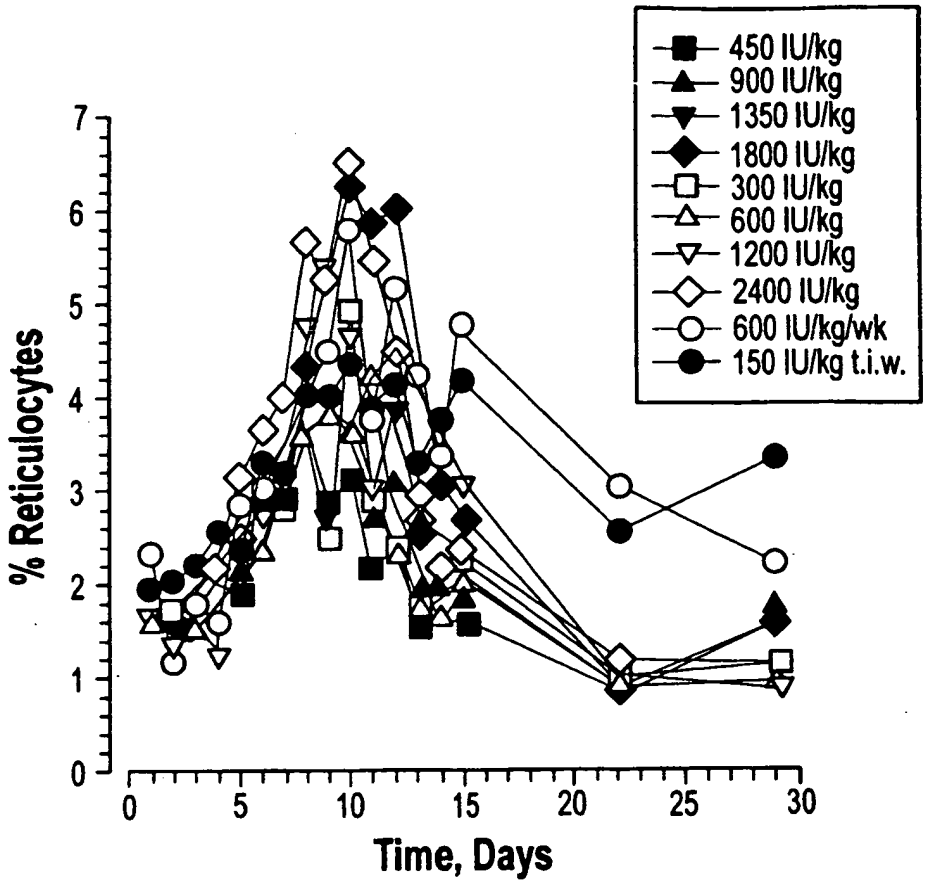

450 IU/kg
900 IU/kg
1350 IU/kg
1800 IU/kg
300 IU/kg
600 IU/kg
1200 IU/kg
2400 IU/kg
600 IU/kg/wk
150 IU/kg t.i.w.
% Reticulocytes
0
1
2
3
4
5
6
7
0
5
10
15
20
25
30
Time, Days

FIG. 27

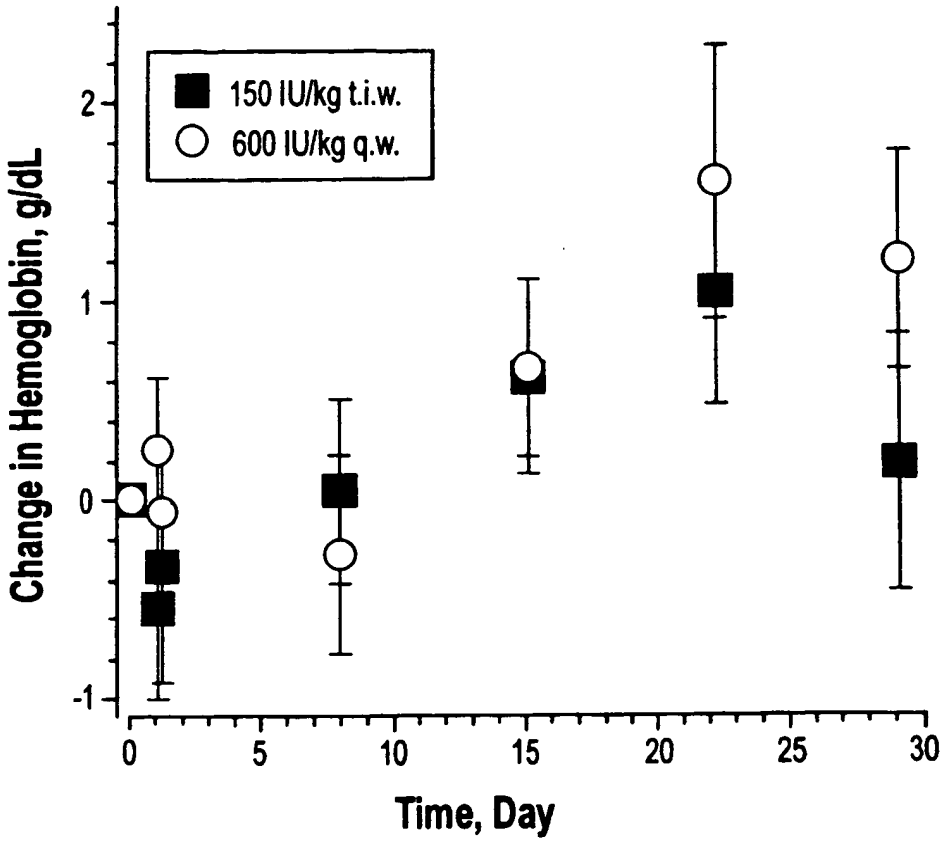

150 IU/kg t.i.w.
600 IU/kg q.w.
Change in Hemoglobin, g/dL
2
1
0
-1
0
5
10
15
20
25
30
Time, Day

FIG. 28

## DEMOGRAPHIC DATA OF SUBJECTS IN CLINICAL STUDY EPO-PHI-370

| TREATMENT | GENDER | WEIGHT (kg) | AGE (yr) | BASELINE HEMOGLOBIN (g/dL) |
|---|---|---|---|---|
| 150 IU/kg t.i.w. | Male | 74.3 ± 8.5 | 32.1 ± 5.5 | 14.7 ± 0.8 |
| | (N = 9) | (63.2-85.0) | (26.0-41.0) | (13.5-15.6) |
| | Female | 62.4 ± 10.3 | 34.6 ± 7.3 | 13.1 ± 0.9 |
| | (N = 15) | (50.5-76.8) | (21.0-46.0) | (11.6-14.8) |
| | Overall | 66.8 ± 11.1 | 33.7 ± 6.7 | 13.7 ± 1.1 |
| | (N = 24) | (50.5-85.0) | (21.0-46.0) | (11.6-15.6) |
| 40,000 IU q.w. | Male | 72.4 ± 7.0 | 32.1 ± 8.6 | 14.6 ± 0.6 |
| | (N = 14) | (61.8-84.5) | (19.0-44.0) | (13.5-15.6) |
| | Female | 65.2 ± 7.8 | 35.1 ± 9.9 | 13.1 ± 0.7 |
| | (N = 8) | (57.3-81.4) | (19.0-45.0) | (11.9-13.9) |
| | Overall | 69.8 ± 8.0 | 33.2 ± 9.0 | 14.1 ± 1.0 |
| | (N = 22) | (57.3-84.5) | (19.0-45.0) | (11.9-15.6) |

FIG. 29

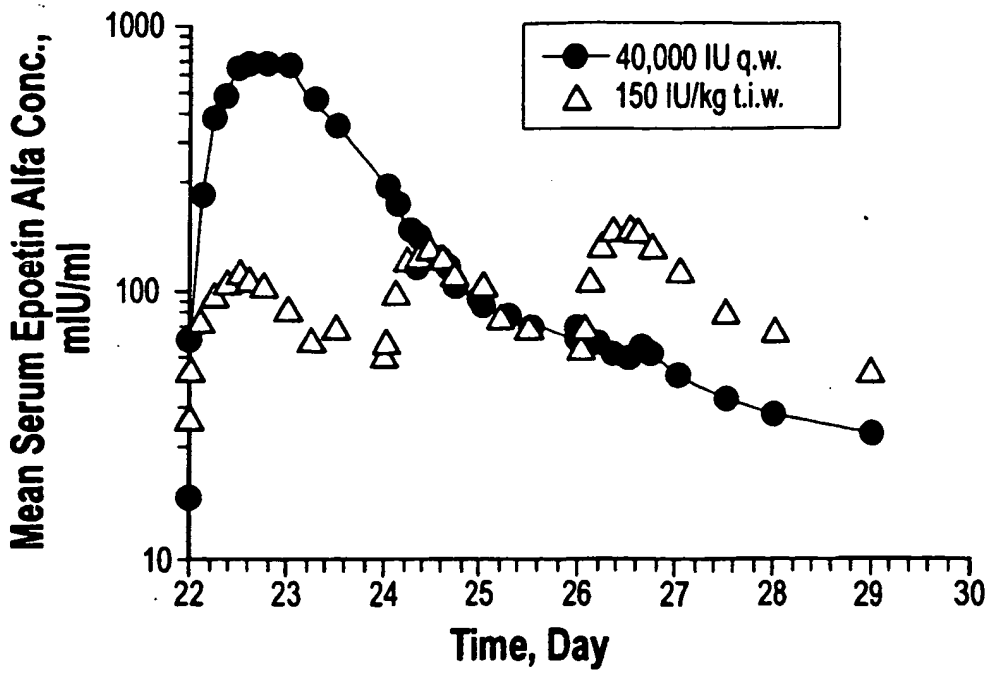

Mean Serum Epoetin Alfa Conc., mIU/ml
1000
100
10
22
23
24
25
26
27
28
29
30
Time, Day
40,000 IU q.w.
150 IU/kg t.i.w.

FIG. 30

## MEAN ± SD (%CV) PHARMACOKINETIC PARAMETERS (PROTOCOL EPO-PHI-370)

| Parameter | 150 (IU/kg t.i.w.) | 40,000 (IU q.w.) | RATIO[a] |
|---|---|---|---|
| $C_{max}$ (mIU/mL) | 191±100 (52.3%) | 785±427 (54.4%) | 4.11 |
| $C_{min}$ (mIU/mL) | 39±18 (45.9%) | 13±9 (73.1%) | 0.33 |
| $t_{max}$ (h) | ND | 18±5 (29.4%) | ND |
| AUC(0-168) (mIU•h/mL) | 13446±4374 (32.5%) | 30084±13516 (44.9%) | 2.24 |
| CL/F (mL/h/kg) | 37.1±12.3 (33.1) | 23.2±10.8 (46.5) | 0.63 |

[a] Parameter ratio of the mean values, 40,000 IU q.w./150 IU/kg t.i.w.
ND = Not Determined

FIG. 31

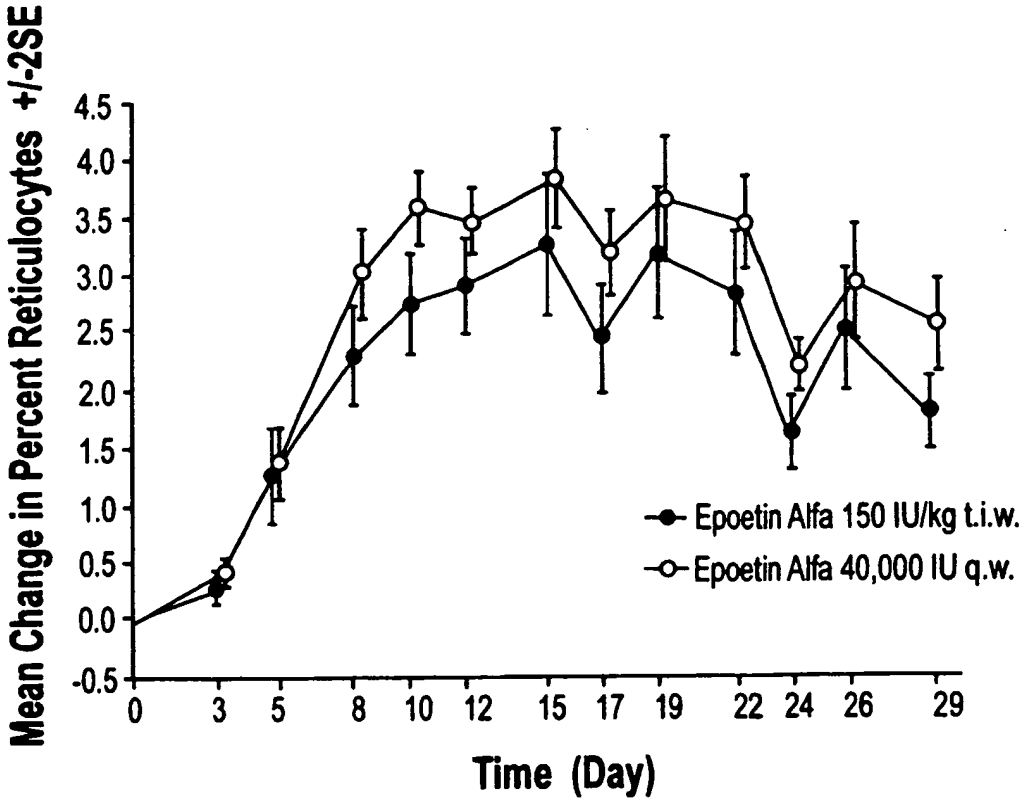

Mean Change in Percent Reticulocytes +/-2SE
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
0
3
5
8
10
12
15
17
19
22
24
26
29
Time (Day)
Epoetin Alfa 150 IU/kg t.i.w.
Epoetin Alfa 40,000 IU q.w.

FIG. 32

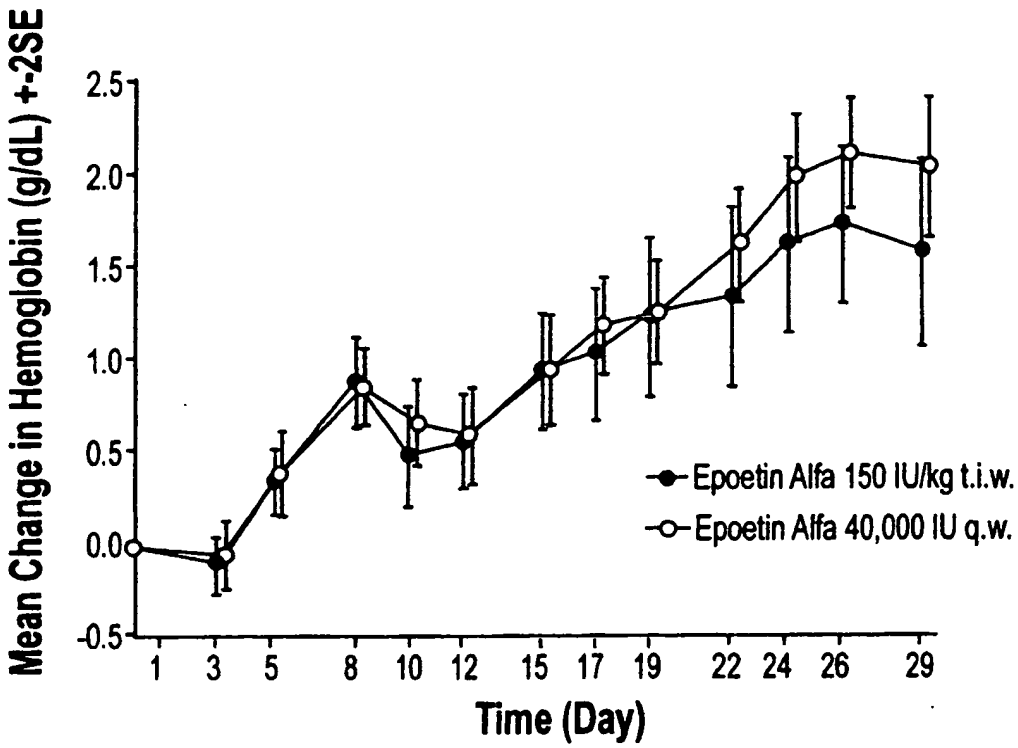

Mean Change in Hemoglobin (g/dL) +-2SE
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1
3
5
8
10
12
15
17
19
22
24
26
29
Time (Day)
Epoetin Alfa 150 IU/kg t.i.w.
Epoetin Alfa 40,000 IU q.w.

FIG. 33

## Mean ± SD (%CV) Pharmacodynamic Parameters Corrected for Baseline Value (Protocol EPO-PHI-370)

| Treatment Group | Auc(RETI)[a] (%·d) | AUC(HEMO)[b] (g·d/dL) | AUC(RBC)[c] (x$10^{12}$cells·d/L) |
|---|---|---|---|
| 150 IU/kg t.i.w. | | | |
| Male | 56.8 ± 21.5 | 26.4 ± 11.6 | 12.0 ± 4.6 |
| (N = 9) | (37.8%) | (43.7%) | (37.8%) |
| Female | 66.6 ± 19.8 | 28.7 ± 18.6 | 12.3 ± 5.5 |
| (N = 15) | (29.7%) | (64.9%) | (44.9%) |
| All Subjects | 62.9 ± 20.5[d] | 27.9 ± 16.1 | 12.2 ± 5.1 |
| (N = 24) | (32.7%) | (57.8%) | (41.7%) |
| 40,000 IU q.w. | | | |
| Male | 75.5 ± 9.8 | 35.3 ± 11.2 | 14.1 ± 4.0 |
| (N = 14) | (12.9%) | (31.8%) | (28.6%) |
| Female | 80.3 ± 10.1 | 23.5 ± 11.5 | 10.9 ± 3.3 |
| (N = 8) | (12.5%) | (48.8%) | (30.6%) |
| All Subjects | 77.2 ± 9.9[d] | 31.0 ± 12.5 | 12.9 ± 4.0 |
| (N = 22) | (12.8%) | (40.3%) | (31.1%) |
| Ratio for All Subjects[e] | 1.23 | 1.11 | 1.06 |
| All Females[f] | 71.3 ± 18.0 | 26.9 ± 16.4 | 11.8 ± 4.9 |
| (N = 23) | (25.3%) | (61.0%) | (41.0%) |
| All Males[g] | 68.2 ± 17.7 | 31.8 ± 12.0 | 13.3 ± 4.3 |
| (N = 23) | (25.9%) | (37.6%) | (32.0%) |

FIG. 34

## Mean ± SD Demographic Data of Subjects in Clinical Study EPO-PHI-373

| Treatment | Gender | Weight (kg) | Age (yr) | Baseline Hemoglobin (g/dL) |
|---|---|---|---|---|
| 150 IU/kg t.i.w. | Male (N = 9) | 72.1 ± 8.2 (64.5-90.5) | 26.4 ± 5.2 (21.0-37.0) | 14.0 ±0.4 (13.2-14.8) |
| | Female (N = 8) | 61.0 ± 4.8 (53.3-66.4) | 24.3 ± 3.5 (20.0-29.0) | 12.8 ± 0.7 (11.7-13.8) |
| | Overall (N = 17) | 66.9 ± 8.7 (53.3-90.5) | 25.4 ± 4.5 (20.0-37.0) | 13.4 ± 0.8 (11.7-14.8) |
| 40,000 IU q.w. | Male (N = 9) | 77.0 ± 12.8 (67.3-106) | 29.4 ± 5.5 (19.0-36.0) | 13.9 ± 0.5 (13.3-14.6) |
| | Female (N = 8) | 63.7 ± 8.8 (51.0-78.0) | 26.5 ± 7.5 (18.0-41.0) | 13.0 ± 0.8 (12.2-14.2) |
| | Overall (N = 17) | 70.7 ± 12.7 (51.0-106) | 28.1 ± 6.5 (18.0-41.0) | 13.5 ± 0.8 (12.2-14.6) |

FIG. 35

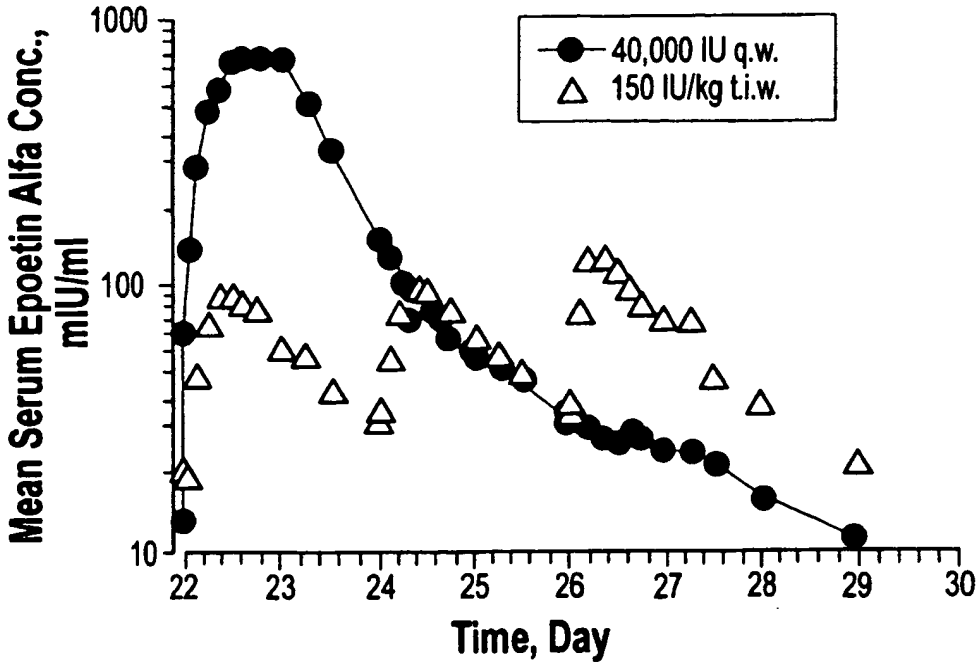

Mean Serum Epoetin Alfa Conc., mIU/ml
1000
100
10
40,000 IU q.w.
150 IU/kg t.i.w.
22
23
24
25
26
27
28
29
30
Time, Day

FIG. 36

## Mean ± SD Pharmacokinetic Parameters (Protocol EPO-PHI-373)

| Parameter | 150 (IU/kg t.i.w.) | 40,000 (IU q.w.) | Ratio[a] |
|---|---|---|---|
| $C_{max}$ (mIU/mL) | 143 ± 54 (37.8%) | 861 ± 445 (51.7%) | 6.02(13.2-14.8) |
| $C_{min}$ (mIU/mL) | 18 ± 9 (50.7%) | 3.8 ± 4.3 (114%) | 0.21 |
| $t_{max}$ (h) | ND | 16 ± 8 (45.6%) | ND |
| AUC(0-168) (mIU·h/mL) | 8587 ± 1521 (17.7%) | 25747 ± 9062 (35.2%) | 3.00 |
| CL/F (mL/h/kg) | 51.4 ± 10.1 (18.7%) | 24.7 ± 7.2 (29.1%) | 0.46 |

[a] Parameter ratio of the mean values, 40,000 IU q.w./150 IU/kg t.i.w.

ND = not determined

FIG. 37

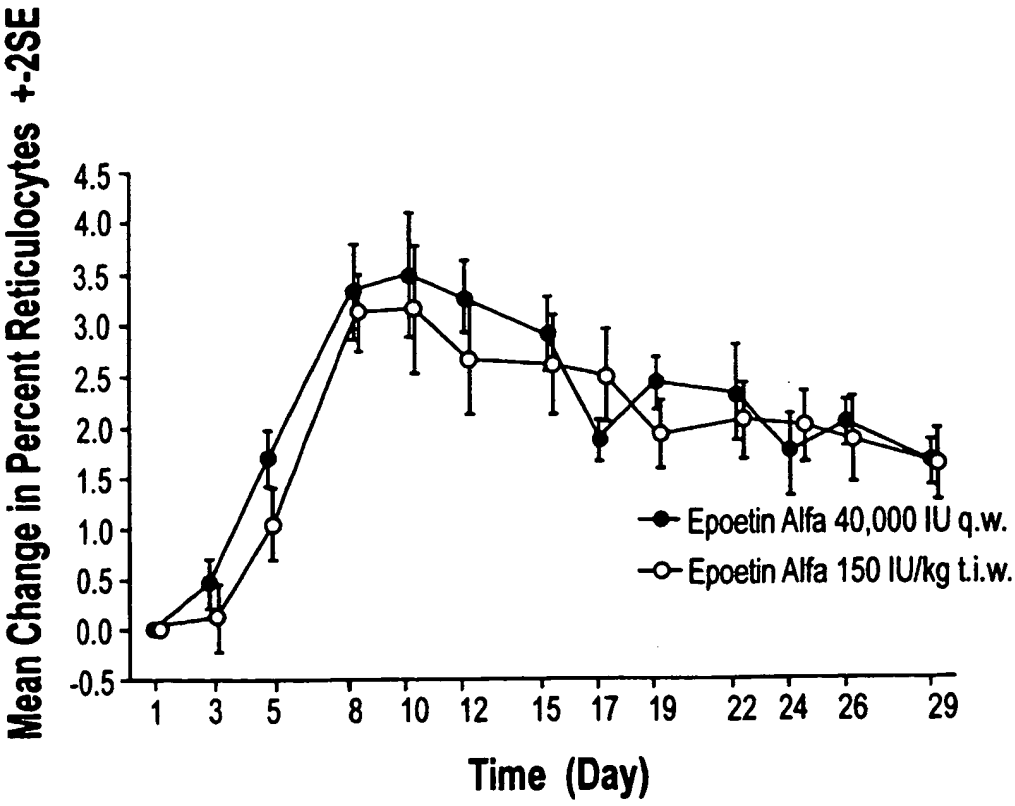

Mean Change in Percent Reticulocytes +-2SE
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1
3
5
8
10
12
15
17
19
22
24
26
29
Time (Day)
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 38

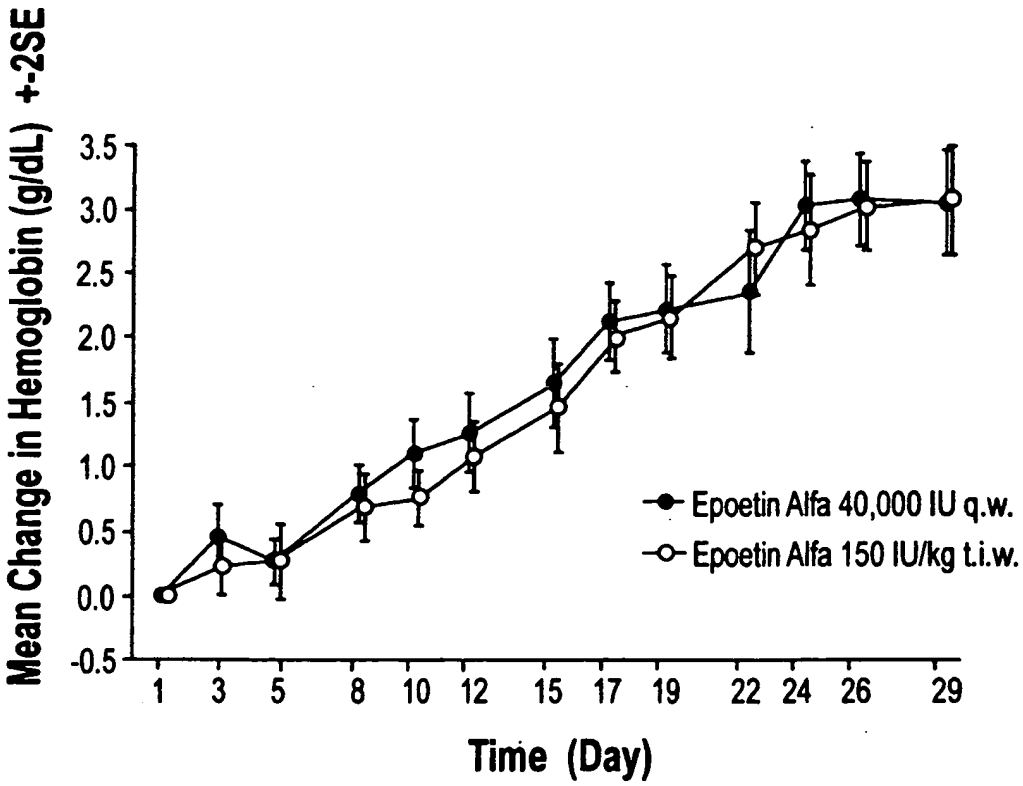

Mean Change in Hemoglobin (g/dL) +-2SE
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1
3
5
8
10
12
15
17
19
22
24
26
29
Time (Day)
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 39

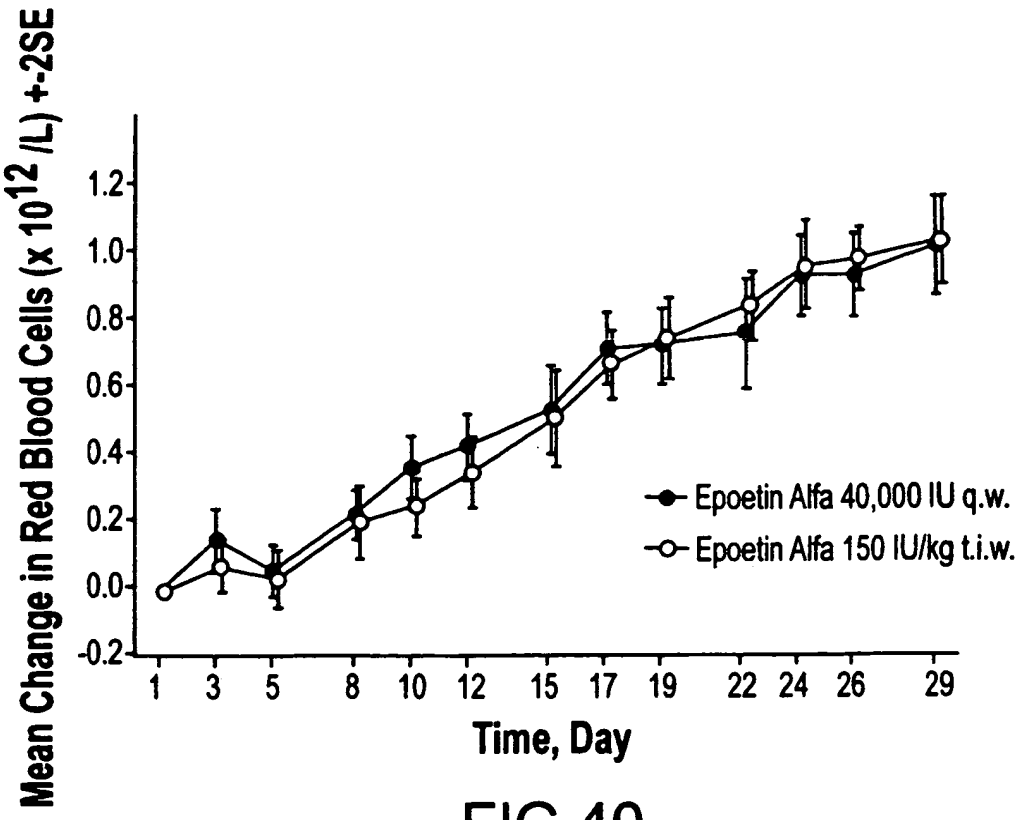

Mean Change in Red Blood Cells (x $10^{12}$ /L) +-2SE
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
1
3
5
8
10
12
15
17
19
22
24
26
29
Time, Day
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG.40

## Mean ± SD (%CV) Pharmacodynamic Parameters Corrected for Baseline Value (Protocol EPO-PHI-373)

| Treatment Group | Auc(RETI)[a] (%·d) | AUC(HEMO)[b] (g·d/dL) | AUC(RBC)[c] ($x10^{12}$·d/L) |
|---|---|---|---|
| 150 IU/kg t.i.w. | | | |
| Male | 55.1 ± 14.4 | 40.4± 13.0 | 13.4± 3.9 |
| (N = 9) | (23.1%) | (32.3%) | (29.3%) |
| Female | 59.6 ± 21.3 | 51.1 ± 10.9 | 16.4 ± 4.4 |
| (N = 8) | (35.7%) | (21.4%) | (26.7%) |
| All Subjects | 57.2 ± 17.5 | 45.4 ± 12.9 | 14.8 ± 4.3 |
| (N = 17) | (30.6%) | (28.5%) | (29.0%) |
| 40,000 IU q.w. | | | |
| Male | 58.8 ± 10.4 | 43.5 ± 11.6 | 13.6 ± 4.3 |
| (N = 9) | (17.7%) | (26.6%) | (31.3%) |
| Female | 68.4 ± 14.4 | 52.4 ± 15.0 | 16.9 ± 4.3 |
| (N = 8) | (21.1%) | (28.6%) | (25.5%) |
| All Subjects | 63.3 ± 13.0 | 47.7 ± 13.6 | 15.1 ± 4.5 |
| (N = 17) | (20.5%) | (28.6%) | (29.5%) |
| Ratio for All Subjects[d] | 1.11 | 1.05 | 1.02 |
| All Females[e] | 64.0 ± 18.1 | 51.7 ± 12.7g | 16.6 ± 4.2g |
| (N = 16) | (28.3%) | (24.5%) | (25.3%) |
| All Males[f] | 57.0 ± 12.3 | 41.9 ± 12.0g | 13.5 ± 4.0g |
| (N = 18) | (21.6%) | (28.7%) | (29.5%) |

FIG. 41

**Mean = SD (%CV) Pharmacokinetic Parameters (Clinical Studies EPO-PHI-358, EPO-PHI-359, EPO-PHI-370, and EPO-PHI-373)**

| Study | Dose | $C_{max}$ (mIU/mL) | $t_{max}$ (h) | AUC[a] (mIU·h/mL) | CL/F (mL/h/kg) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| Single Subcutaneous Dose Administration | | | | | | |
| EPO359 | 300 IU/kg | 429 ± 86 (20.0%) | 22.8 ± 8.1 (36.5%) | 20056 ± 4138 (20.6%) | 15.5 ± 3.1 (20.2%) | 68.2 ± 52.2 (76.6%) |
| EPO358 | 450 IU/kg | 1263 ± 290 (23.0%) | 15.6 ± 5.8 (37.0%) | 45498 ± 12342 (27.1%) | 10.4 ± 2.6 (24.9%) | 24.2 ± 3.2 (13.2%) |
| EPO359 | 600 IU/kg | 1263 ± 486 (38.5%) | 27.6 ± 9.1 (33.0%) | 55475 ± 16384 (29.5%) | 11.8 ± 4.2 (35.5%) | 29.3 ± 9.4 (32.0%) |
| EPO358 | 900 IU/kg | 2235 ± 599 (26.8%) | 22.2 ± 12.7 (57.0%) | 103154 ± 28024 (27.2%) | 9.36 ± 2.97 (31.7%) | 36.0 ± 13.5 (37.3%) |
| EPO359 | 1200 IU/kg | 2256 ± 710 (31.4%) | 26.4 ± 7.8 (29.4%) | 119932 ± 44217 (36.9%) | 11.2 ± 4.2 (37.7%) | 78.5 ± 95.4 (122%) |
| EPO358 | 1350 IU/kg | 3755 ± 879 (23.4%) | 23.4 ± 8.8 (37.8%) | 174193 ± 41417 (23.8%) | 8.23 ± 2.57 (31.3%) | 33.4 ± 2.4 (7.2%) |
| EPO358 | 1800 IU/kg | 4370 ± 1673 (38.3%) | 28.8 ± 7.8 (27.2%) | 258600 ± 101175 (39.1%) | 7.64 ± 2.22 (29.1%) | 32.4 ± 8.4 (25.9%) |
| EPO359 | 2400 IU/kg | 6819 ± 764 (11.2%) | 25.2 ± 6.2 (24.7%) | 429441 ± 32139 (7.5%) | 5.61 ± 0.44 (7.8%) | 43.6 ± 25.9 (59.5%) |
| Multiple Subcutaneous Dose Administration | | | | | | |
| EPO358 Wk 4 | 150 IU/kg t.i.w. | 252 ± 71 (28.0%) | NA | 16582 ± 4256 (25.7%) | 28.7 ± 7.8 (27.1%) | 25.9 ± 7.1 (27.2%) |
| EPO359 Wk 1 | 600 IU/kg q.w. | 1502 ± 384 (25.6%) | 21.6 ± 6.1 (28.5%) | 63439 ± 10893 (17.2%) | 9.70 ± 1.8 (18.1%) | 28.3 ± 7.5 (26.3%) |
| EPO359 Wk 4 | 600 IU/kg q.w. | 1278 ± 213 (16.6%) | 24.0 ± 8.7 (36.4%) | 50725 ± 6774 (13.4%) | 12.0 ± 1.6 (13.2%) | 28.1 ± 7.0 (24.9%) |

FIG. 42

| Applicant: | The R.W. Johnson Pharmaceutical Research Institute | | | | | |
|---|---|---|---|---|---|---|
| Drug: | Epoetin Alfa Once Weekly Dosing | | | | | |
| NDA No.: | Insert NDA No. | | | | | |
| Study | Dose | $C_{max}$ (mIU/mL) | $t_{max}$ (h) | AUC[a] (mIU·h/mL) | CL/F (mL/h/kg) | $t_{1/2}$ (h) |
| Single Subcutaneous Dose Administration | | | | | | |
| EPO370 Wk 4 | 150 IU/kg t.i.w. | 191 ± 100 (52.3%) | NA | 13446 ± 4374 (32.5%) | 37.1 ± 12.3 (33.1%) | 31.8 ± 13.4 (42.1%) |
| EPO370 Wk 4 | 40,000 IU q.w. | 785 ± 427 (54.4%0) | 18 ± 5 (29.4%) | 30084 ± 13516 (44.9%) | 23.2 ± 10.8 (46.5%) | 39.3 ± 7.1 (18.1%) |
| EPO373 Wk 4 | 150 IU/kg t.i.w. | 143 ± 54 (37.8%) | NA | 8587 ± 1521 (17.7%) | 54.1 ± 10.1 (18.7%) | 19.4 ± 8.1 (41.5%) |
| EPO373 Wk 4 | 40,000 IU q.w. | 861 ± 445 (51.7%) | 16 ± 8 (45.6%) | 25.747 ± 9062 (35.2%) | 24.7 ± 7.2 (29.1%) | 15.0 ± 6.1 (40.9%) |

[a] AUC(0-168) during a dose week for multiple dose regimens and AUC(0-672) during the 4-wk of study period for single doses.

NA = Not applicable

FIG. 42

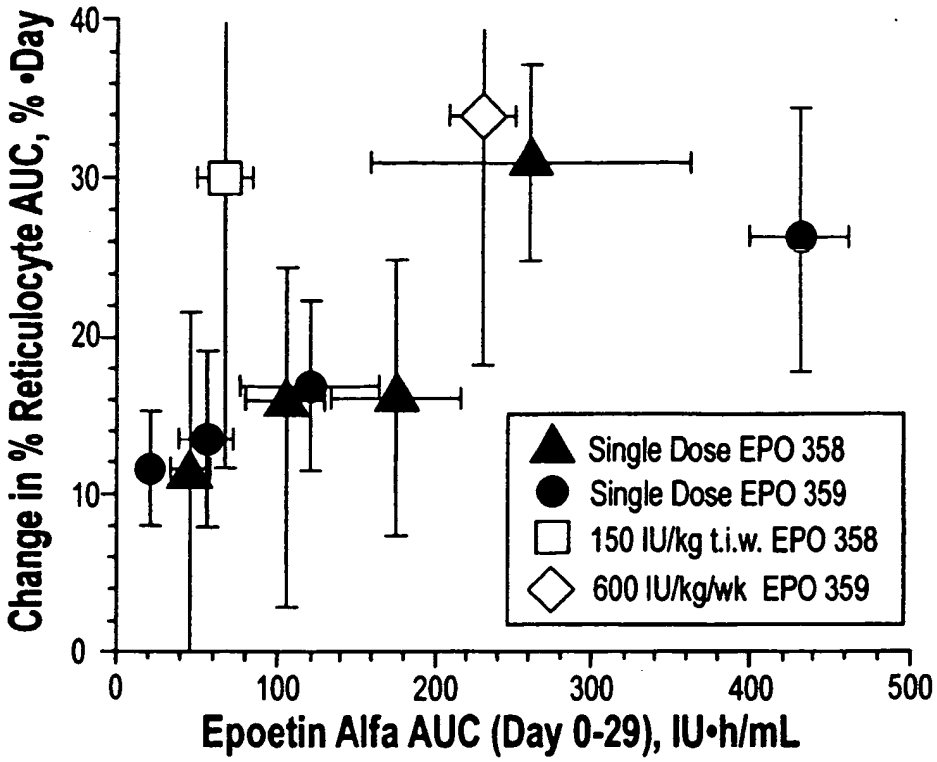

Change in % Reticulocyte AUC, % •Day
Epoetin Alfa AUC (Day 0-29), IU•h/mL
0
10
20
30
40
0
100
200
300
400
500
Single Dose EPO 358
Single Dose EPO 359
150 IU/kg t.i.w. EPO 358
600 IU/kg/wk EPO 359

FIG. 43

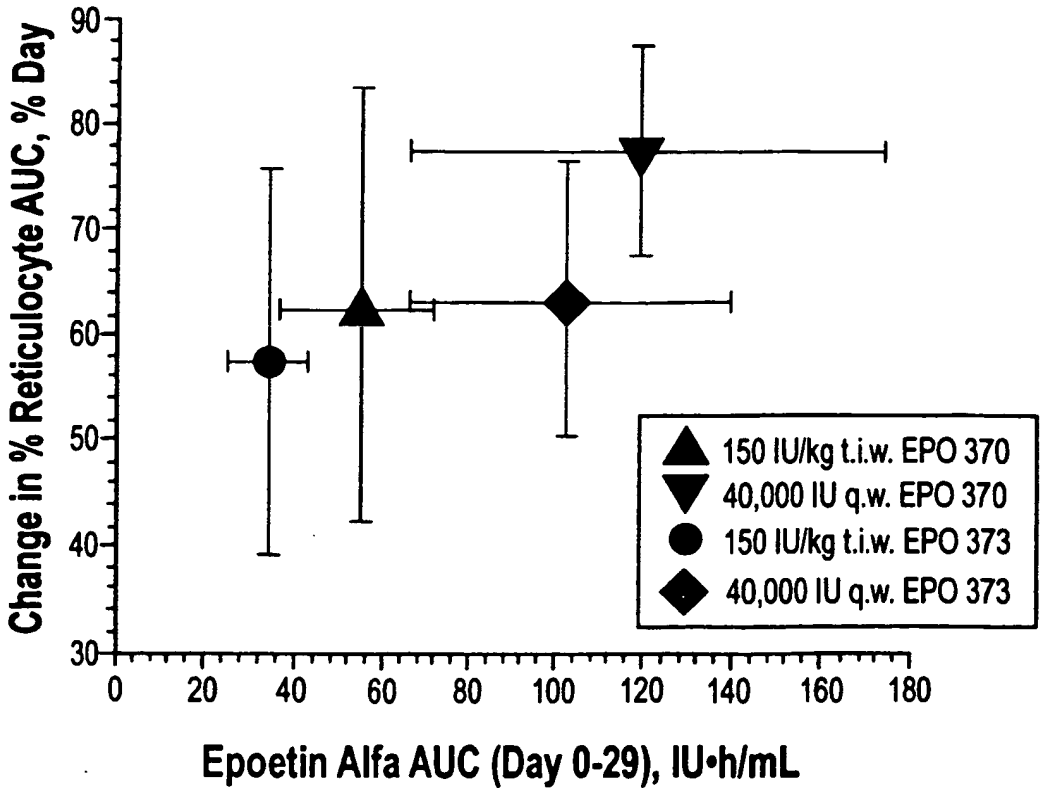

Change in % Reticulocyte AUC, % Day
90
80
70
60
50
40
30
0
20
40
60
80
100
120
140
160
180
Epoetin Alfa AUC (Day 0-29), IU•h/mL
150 IU/kg t.i.w. EPO 370
40,000 IU q.w. EPO 370
150 IU/kg t.i.w. EPO 373
40,000 IU q.w. EPO 373

FIG. 44

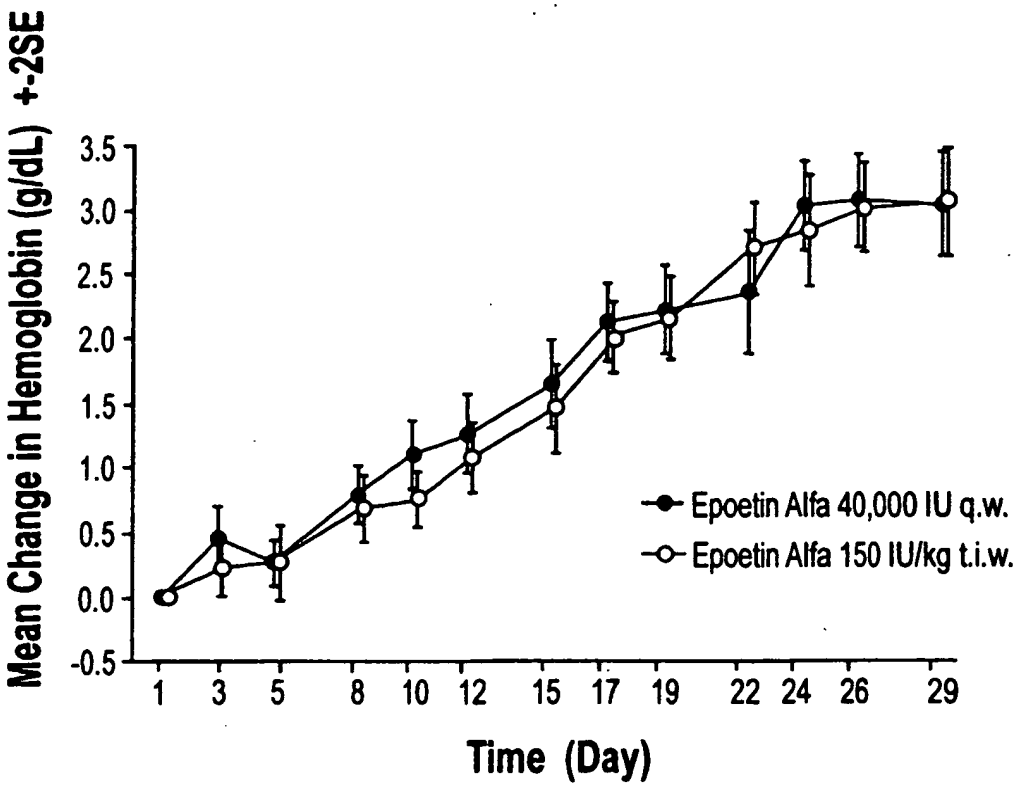

Mean Change in Hemoglobin (g/dL) +-2SE
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1
3
5
8
10
12
15
17
19
22
24
26
29
Time (Day)
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 45

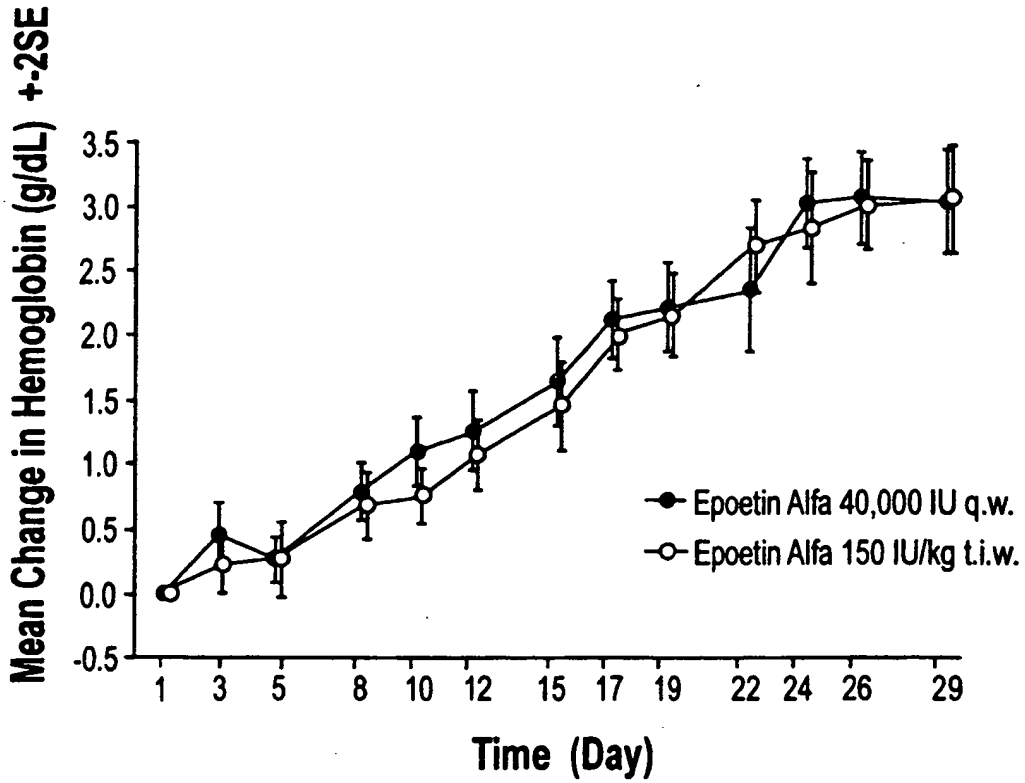

Mean Change in Hemoglobin (g/dL) +-2SE
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1
3
5
8
10
12
15
17
19
22
24
26
29
Time (Day)
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 46

## Demographic and Baseline Characteristics (All Subjects in Protocol EPO-PHI-373)

| Characteristic | Epoetin Alfa 150 IU/kg t.i.w. (N=18) | Epoetin Alfa 40,000 IU q.w. (N=18) | Total (N=36) |
|---|---|---|---|
| **Sex** | | | |
| Male | 9 (50%) | 9 (50%) | 18 (50%) |
| Female | 9 (50%) | 9 (50%) | 18 (50%) |
| **Age (years)** | | | |
| Mean (SD) | 25.3 (4.34) | 27.7 (6.48) | 26.5 (5.57) |
| Median | 24 | 27.5 | 25.0 |
| Range | 20.0-37.0 | 18.0-41.0 | 18.0-41.0 |
| **Weight (kg)** | | | |
| Mean (SD) | 66.8 (8.47) | 70.3 (12.51) | 68.6 (10.67) |
| Median | 66.0 | 69.0 | 67.3 |
| Range | 53.3-90.5 | 51.0-105.5 | 51.0-105.5 |
| **Height (cm)** | | | |
| Mean (SD) | 171.9 (6.94) | 170.9 (8.86) | 171.4 (7.86) |
| Median | 172.8 | 169.5 | 171.8 |
| Range | 160.5-191.0 | 160.5-191.0 | 160.5-191.0 |
| **Race** | | | |
| White | 17 (94%) | 15 (83%) | 32 (89%) |
| Black | 1 (6%) | 2 (11%) | 3 (8%) |
| Other | 0 (0%) | 1 (6%) | 1 (3%) |

FIG. 47

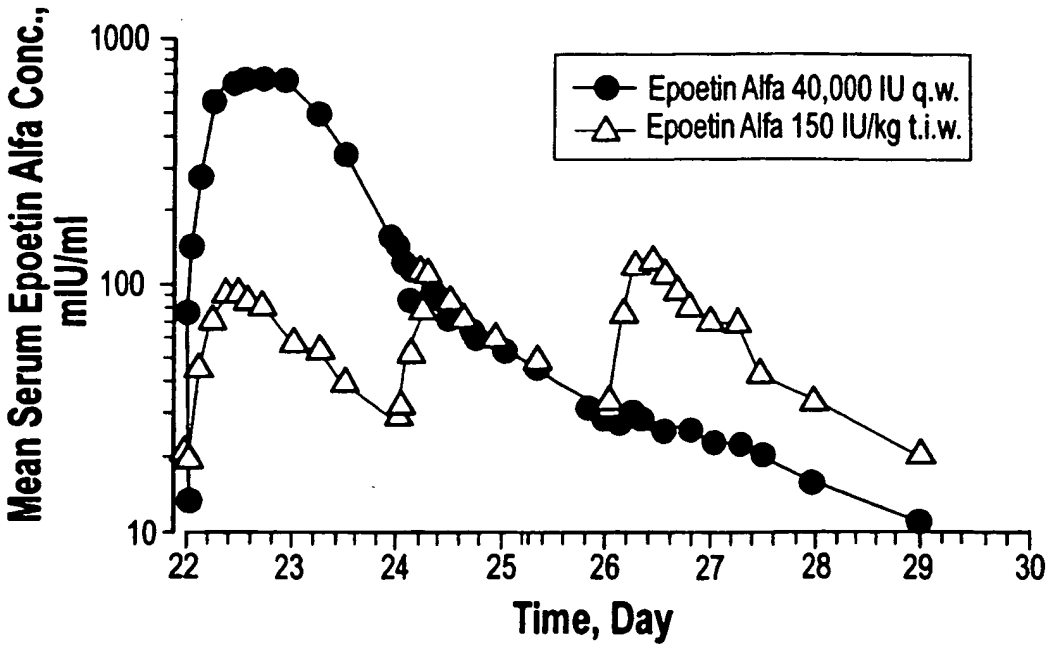

Mean Serum Epoetin Alfa Conc., mIU/ml
1000
100
10
22
23
24
25
26
27
28
29
30
Time, Day
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 48

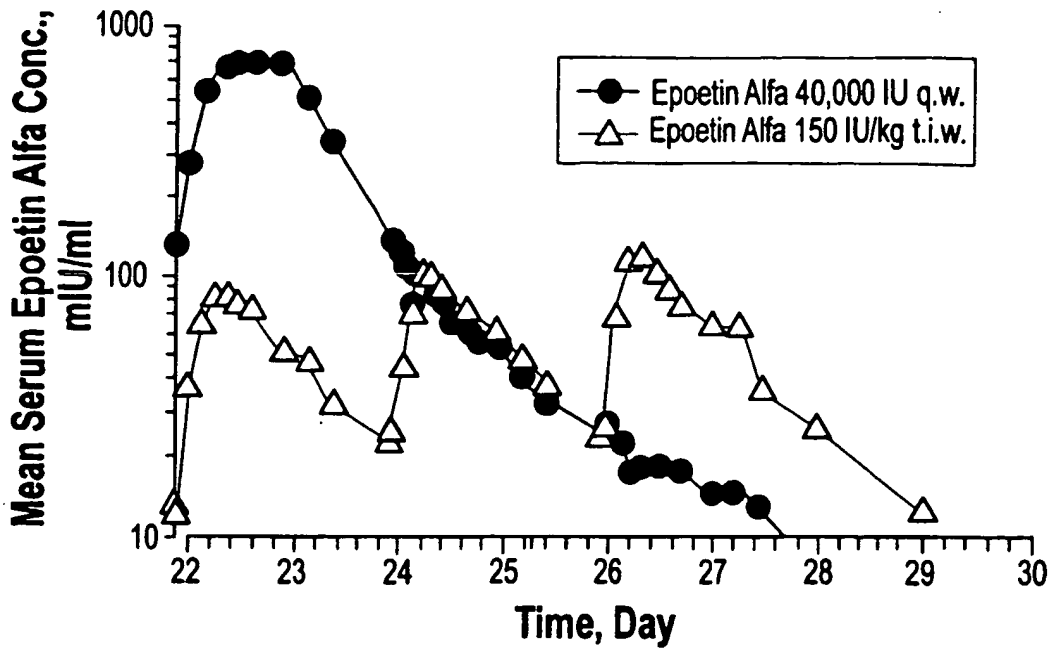

Mean Serum Epoetin Alfa Conc., mIU/ml
1000
100
10
22
23
24
25
26
27
28
29
30
Time, Day
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 49

## SELECTED MEAN (SD) [%CV] PHARMACOKINETIC PARAMETERS (SUBJECTS IN THE EFFICACY POPULATION IN PROTOCOL EPO-PHI-373)

| | 150 IU/kg t.i.w. (n=17) | | 40,000 IU q.w. (n-17) | | |
|---|---|---|---|---|---|
| Parameter | Mean (SD) | [%CV] | Mean (SD) | [%CV] | Ratio[a] |
| $C_{max}$ (mIU/mL) | 143 (54) | [37.8%] | 861 (445) | [51.7%] | 6.02 |
| $C_{min}$ (mIU/mL) | 18 (9) | [50.7%] | 3.8 (4.3) | [114%] | 0.21 |
| $t_{max}$ (h) | ND | | 16 (8) | [45.6%] | ND |
| $AUC_{(0\text{-}168)}$ (mIU•h/mL) | 8587 (1521) | [17.7%] | 25747 (9062) | [35.2%] | 3.00 |
| CL/F (mL/h/kg) | 54.1 (10.1) | [18.7%] | 24.7 (7.2) | [29.1%] | 0.46 |

[a] Parameter ratio of the mean values, 40,000 IU q.w./150 IU/kg t.i.w.
ND = Not determined

FIG. 50

## MEAN (SD) CHANGE FROM BASELINE IN PERCENT RETICULOCYTES (SUBJECTS IN THE EFFICACY POPULATION-PROTOCOL EPO-PHI-373)

| | Epoetin Alfa 150 IU/kg t.i.w. | | | Epoetin Alfa 40,000 IU/kg q.w. | | |
|---|---|---|---|---|---|---|
| | N | Mean (SD) | Range | N | Mean (SD) | Range |
| **Baseline** | 17 | 1.5 (0.59) | 0.9-2.9 | 17 | 1.4 (0.45) | 0.8-2.5 |
| **Change from Baseline to Day** | | | | | | |
| Day 3 | 17 | 1.1 (0.68) | -2.0-1.3 | 17 | 0.5 (0.51) | -0.3-1.8 |
| Day 5 | 17 | 1.1 (0.76) | -1.0-2.2 | 17 | 1.7 (0.56) | 0.5-2.7 |
| Day 8 | 17 | 3.1 (0.77) | 1.9-4.3 | 17 | 3.3 (0.97) | 2.0-5.3 |
| Day 10 | 17 | 3.2 (1.30) | 1.8-5.5 | 17 | 3.5 (1.26) | 1.4-6.8 |
| Day 12 | 17 | 2.7 (1.12) | 0.3-5.4 | 17 | 3.3 (0.74) | 2.0-5.5 |
| Day 15 | 17 | 2.6 (1.02) | 1.0-4.8 | 17 | 2.9 (0.76) | 1.6-4.9 |
| Day 17 | 17 | 2.5 (0.94) | -1.7-5.4 | 17 | 1.9 (0.42) | 1.3-2.7 |
| Day 19 | 17 | 1.9 (0.74) | -0.0-3.4 | 17 | 2.4 (0.53) | 1.7-3.6 |
| Day 22 | 17 | 2.1 (0.78) | -0.1-2.9 | 17 | 2.4 (1.00) | 0.7-4.5 |
| Day 24 | 17 | 2.0 (0.73) | 0.3-3.1 | 16 | 1.7 (0.82) | -0.0-3.2 |
| Day 26 | 17 | 1.9 (0.90) | -0.3-4.0 | 17 | 2.1 (0.47) | 1.0-2.7 |
| Day 29 | 17 | 1.7 (0.74) | -0.3-3.2 | 17 | 1.7 (0.46) | 1.0-2.7 |
| Last Visit | 17 | 1.7 (0.74) | -0.3-3.2 | 17 | 1.7 (0.46) | 1.0-2.7 |

FIG. 51

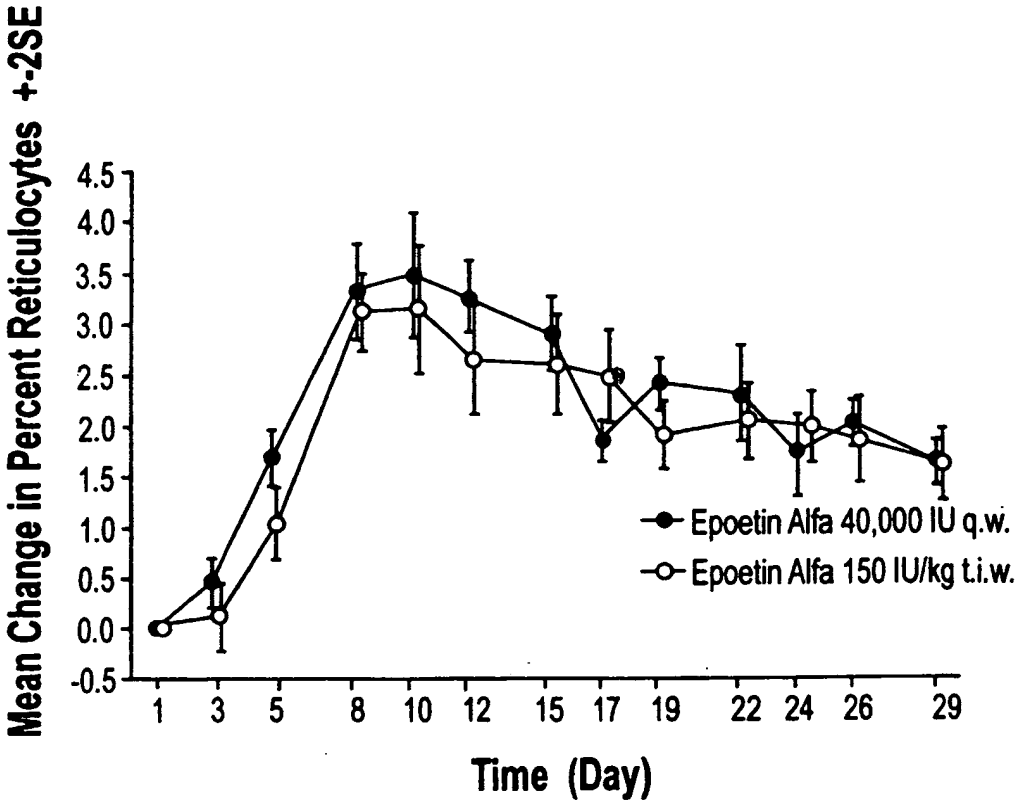

Mean Change in Percent Reticulocytes +-2SE
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1
3
5
8
10
12
15
17
19
22
24
26
29
Time (Day)
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 52

## MEAN (SD) CHANGE FROM BASELINE IN HEMOGLOBIN (g/dL) (SUBJECTS IN THE EFFICACY POPULATION-PROTOCOL EPO-PHI-373)

| | Epoetin Alfa 150 IU/kg t.i.w. | | | Epoetin Alfa 40,000 IU/kg q.w. | | |
|---|---|---|---|---|---|---|
| | N | Mean (SD) | Range | N | Mean (SD) | Range |
| **Baseline** | 17 | 13.4 (0.81) | 11.7-14.8 | 17 | 13.5 (0.79) | 12.2-14.6 |
| **Change from Baseline to Day** | | | | | | |
| Day 3 | 17 | 0.2 (0.45) | -0.5-1.1 | 17 | 0.5 (0.52) | -0.5-1.5 |
| Day 5 | 17 | 1.3 (0.63) | -0.6-1.8 | 17 | 0.3 (0.37) | -0.4-0.8 |
| Day 8 | 17 | 0.7 (0.54) | -0.4-1.8 | 17 | 0.8 (0.47) | 1.0-1.7 |
| Day 10 | 17 | 0.8 (0.45) | -0.2-1.5 | 17 | 1.1 (0.56) | 0.2-2.4 |
| Day 12 | 17 | 1.1 (0.57) | 0.4-2.2 | 17 | 1.3 (0.65) | 0.1-2.4 |
| Day 15 | 17 | 1.5 (0.72) | 0.2-2.4 | 17 | 1.7 (0.73) | 0.2-2.7 |
| Day 17 | 17 | 2.0 (0.57) | 1.0-3.0 | 17 | 2.1 (0.62) | 1.0-3.2 |
| Day 19 | 17 | 2.2 (0.68) | 1.2-3.2 | 17 | 2.2 (0.69) | 1.2-3.2 |
| Day 22 | 17 | 2.7 (0.74) | 1.4-3.9 | 17 | 2.4 (1.00) | 0.7-4.7 |
| Day 24 | 17 | 2.9 (0.90) | 0.7-4.2 | 16 | 3.0 (0.70) | 1.6-4.0 |
| Day 26 | 17 | 3.0 (0.69) | 1.8-4.3 | 17 | 3.1 (0.74) | 1.9-4.4 |
| Day 29 | 17 | 3.1 (0.86) | 1.4-4.5 | 17 | 3.1 (0.84) | 1.8-4.6 |
| Last Visit | 17 | 3.1 (0.86) | 1.4-4.5 | 17 | 3.1 (0.84) | 1.8-4.6 |

FIG. 53

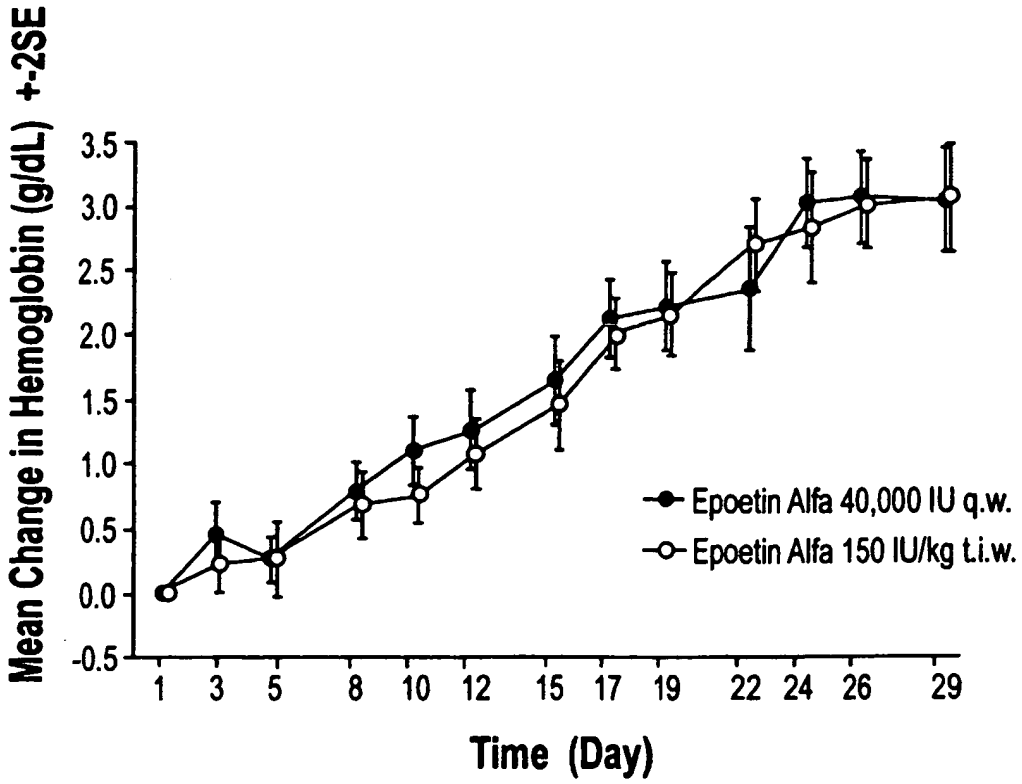

Mean Change in Hemoglobin (g/dL) +-2SE
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1
3
5
8
10
12
15
17
19
22
24
26
29
Time (Day)
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 54

## MEAN (SD) CHANGE FROM BASELINE IN RED BLOOD CELLS ($x10^{12}$/L) (SUBJECTS IN THE EFFICACY POPULATION-PROTOCOL EPO-PHI-373)

| | Epoetin Alfa 150 IU/kg t.i.w. | | | Epoetin Alfa 40,000 IU/kg q.w. | | |
|---|---|---|---|---|---|---|
| | N | Mean (SD) | Range | N | Mean (SD) | Range |
| **Baseline** | 17 | 4.4 (0.30) | 3.8-5.1 | 17 | 4.4 (0.26) | 4.0-4.8 |
| **Change from Baseline to Day** | | | | | | |
| Day 3 | 17 | 0.1 (0.16) | -0.2-0.4 | 17 | 0.2 (0.19) | -0.2-0.5 |
| Day 5 | 17 | 0.0 (0.18) | -0.2-0.4 | 17 | 0.1 (0.15) | -0.2-0.3 |
| Day 8 | 17 | 0.2 (0.21) | -0.2-0.8 | 17 | 0.2 (0.14) | 0.0-0.5 |
| Day 10 | 17 | 0.2 (0.17) | -0.1-0.5 | 17 | 0.4 (0.18) | 0.1-0.8 |
| Day 12 | 17 | 0.3 (0.21) | -0.1-0.7 | 17 | 0.4 (0.20) | -0.0-0.7 |
| Day 15 | 17 | 0.5 (0.29) | 0.0-0.9 | 17 | 0.5 (0.27) | -0.1-0.9 |
| Day 17 | 17 | 0.7 (0.20) | 0.3-1.0 | 17 | 0.7 (0.21) | 0.4-1.1 |
| Day 19 | 17 | 0.7 (0.24) | 0.3-1.1 | 17 | 0.7 (0.22) | 0.3-1.1 |
| Day 22 | 17 | 0.8 (0.20) | 0.5-1.2 | 17 | 0.8 (0.34) | 0.2-1.4 |
| Day 24 | 17 | 1.0 (0.28) | 0.3-1.3 | 16 | 0.9 (0.23) | 0.4-1.2 |
| Day 26 | 17 | 1.0 (0.18) | 0.7-1.3 | 17 | 0.9 (0.25) | 0.4-1.3 |
| Day 29 | 17 | 1.0 (0.27) | 0.5-1.4 | 17 | 1.0 (0.30) | 0.4-1.4 |
| Last Visit | 17 | 1.0 (0.27) | 0.5-1.4 | 17 | 1.0 (0.30) | 0.4-1.4 |

FIG. 55

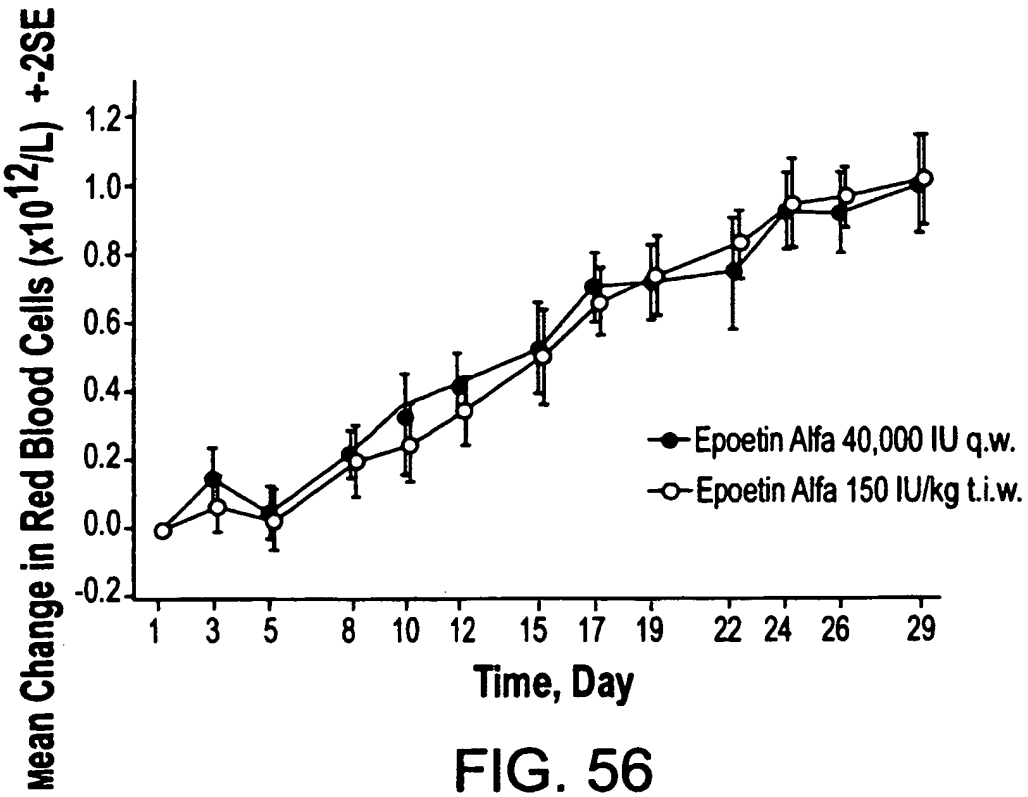

Mean Change in Red Blood Cells (x10^12/L) +-2SE
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
1
3
5
8
10
12
15
17
19
22
24
26
29
Time, Day
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 56

# MEAN (SD) [%CV] PHARMACODYNAMIC PARAMETERS CORRECTED FOR BASELINE VALUE (EFFICACY POPULATION IN PROTOCOL EPO-PHI-373)

| | AUC(RETI)[a] (%.d) | | AUC(HEMO)[b] (g.d/dL) | | AUC(RBC)[c] ($x10^{12}$.d/L) | |
|---|---|---|---|---|---|---|
| TREATMENT GROUP | MEAN (SD) | [%CV] | MEAN (SD) | [%CV] | MEAN (SD) | [%CV] |
| **150 IU/kg t.i.w.** | | | | | | |
| Male (N=9) | 55.1 (14.4) | [26.1%] | 40.4 (13.0) | [32.2%] | 13.4 (3.9) | [29.3%] |
| Female (N=8) | 59.6 (21.3) | [35.7%] | 51.1 (10.9) | [21.4%] | 16.4 (4.4) | [26.7%] |
| All Subjects (N=17) | 57.2 (17.5) | [30.6%] | 45.4 (12.9) | [28.5%] | 14.8 (4.3) | [29.0%] |
| **40,000 IU q.w.** | | | | | | |
| Male (N=9) | 58.8 (10.4) | [17.7%] | 43.5 (1 | 1.6) [26.6%] | 13.6 (4.3) | [31.3%] |
| Female (N=8) | 68.4 (14.4) | [21.1%] | 52.4 (15.0) | [28.6%] | 16.9 (4.3) | [25.5%] |
| All Subjects (N=17) | 63.3 (13.0) | [20.5%] | 47.7 (13.6) | [28.6%] | 15.1 (4.5) | [29.5%] |
| Ratio for All Subjects[d] | 1.1 | 1 | 1.05 | | 1.02 | |
| All Females[e] (N=16) | 64.0 (18.1) | [28.3%] | 51.7 (12.7) | [g] [24.5%] | 16.6 (4.2) | [g] [25.3%] |
| All Males[f] (N=18) | 57.0 (12.3) | [21.6%] | 41.9 (12.0) | [g] [28.7%] | 13.5 (4.0) | [g] [29.5%] |

%CV = percent coefficient of variation

[a] AUC of % reticulocytes over the one month study period and corrected for predose baseline value.

[b] AUC of hemoglobin over the one month study period and corrected for predose baseline value.

[c] AUC of red blood cells over the one month study period and corrected for predose baseline value.

[d] Ratios of 40,000 IU q.w. to 150 IU/kg t.i.w. mean parameter values for all subjects.

[e] Including all female subjects in both treatment groups.

[f] Including all male subjects in both treatment groups.

[g] Statistically different ($p<0.05$) between male and female subjects

FIG. 57

| Body System<br>Preferred Term | Epoetin Alfa 150 IU/kg t.i.w. (N=18) | Epoetin Alfa 40,000 IU q.w. (N=18) |
|---|---|---|
| Any adverse event | 13 (72%) | 12 (67%) |
| Body as a whole - general disorders | 6 (33%) | 7 (39%) |
| Pain | 4 (22%) | 5 (28%) |
| Fatigue | 2 (11%) | 1 (6%) |
| Enlarged abdomen | 1 (6%) | 0 (0%) |
| Allergic reaction | 0 (0%) | 1 (6%) |
| Back pain | 0 (0%) | 1 (6%) |
| Center & periph nerv syst disorders | 6 (33%) | 6 (33%) |
| Headache | 5 (28%) | 5 (28%) |
| Dizziness | 1 (6%) | 2 (11%) |
| Hyperesthesia | 1 (6%) | 0 (0%) |
| Hypertonia | 1 (6%) | 0 (0%) |
| Skin and appendage disorders | 6 (33%) | 3 (17%) |
| Erythematous rash | 5 (28%) | 2 (11%) |
| Rash | 2 (11%) | 1 (6%) |
| Skin disorder | 0 (0%) | 1 (6%) |
| Localized skin reaction | 1 (6%) | 0 (0%) |
| Gastro-intestinal system disorders | 4 (22%) | 2 (11%) |
| Abdominal pain | 2 (11%) | 0 (0%) |
| Nausea | 2 (11%) | 0 (0%) |
| Constipation | 1 (6%) | 0 (0%) |
| Diarrhea | 1 (6%) | 0 (0%) |
| Gastroenteritis | 0 (0%) | 1 (6%) |
| Gingivitis | 0 (0%) | 1 (6%) |
| Toothache | 1 (6%) | 0 (0%) |
| Application site disorders | 5 (28%) | 1 (6%) |
| Injection site bruising | 3 (17%) | 1 (6%) |
| Application site reaction | 2 (11%) | 0 (0%) |
| Injection site pain | 1 (6%) | 0 (0%) |
| Respiratory system disorders | 2 (11%) | 1 (6%) |
| Upper respiratory tract infection | 2 (11%) | 0 (0%) |
| Pharyngitis | 0 (0%) | 1 (6%) |
| Rhinitis | 0 (0%) | 1 (6%) |
| Metabolic nutritional disorders | 1 (6%) | 1 (6%) |
| Thirst | 1 (6%) | 0 (0%) |
| Xerophthalmia | 0 (0%) | 1 (6%) |
| Musculo-skeletal system disorders | 2 (11%) | 0 (0%) |
| Myalgia | 1 (6%) | 0 (0%) |
| Skeletal pain | 1 (6%) | 0 (0%) |
| Psychiatric disorders | 0 (0%) | 2 (11%) |
| Insomnia | 0 (0%) | 1 (6%) |
| Somnolence | 0 (0%) | 1 (6%) |

FIG. 58

| Body System<br>Preferred Term | Epoetin Alfa<br>150 IU/kg t.i.w.<br>(N=18) | Epoetin Afa<br>40,000 IU q.w.<br>(N=18) |
|---|---|---|
| Heart rate and rhythm disorders | 0 (0%) | 1 (6%) |
| Palpitation | 0 (0%) | 1 (6%) |
| Female reproductive disorders | 1 (11%)* | 0 (0%) |
| Dysmenorrhea | 1 (11%)* | 0 (0%) |
| Other special senses disorders | 1 (6%) | 0 (0%) |
| Taste perversion | 1 (6%) | 0 (0%) |
| Vascular (extracardiac) disorders | 1 (6%) | 0 (0%) |
| Phlebitis | 1 (6%) | 0 (0%) |
| Vision disorders | 1 (6%) | 0 (0%) |
| Conjunctivitis | 1 (6%) | 0 (0%) |

* Percentages taken as a percentage of the



FIG. 58

## Mean (SD) Change from Baseline in Iron Profile (All Subjects in Protocol EPO-PHI-373)

| | Epoetin Alfa 150 IU/kg t.i.w. | | | Epoetin Alfa 40,000 IU q.w. | | |
|---|---|---|---|---|---|---|
| | N | Mean | (SD) | N | Mean | (SD) |
| **Serum Iron (µg/dL)** | | | | | | |
| Baseline | 18 | 97.1 | (40.54) | 18 | 102.7 | (27.23) |
| Change from Baseline to Day 8 | 18 | 7.1 | (79.56) | 18 | 28.8 | (95.05) |
| Change from Baseline to Day 15 | 18 | 34.7 | (122.43) | 17 | 49.6 | (106.89) |
| Change from Baseline to Day 22 | 18 | 21.4 | (108.34) | 17 | 23.6 | (95.73) |
| Change from Baseline to Day 29 | 17 | -44.3 | (43.76) | 18 | 22.0 | (78.18) |
| Change from Baseline to Last Visit | 18 | -33.5 | (62.59) | 18 | 22.0 | (78.18) |
| **Ferritin (ng/mL)** | | | | | | |
| Baseline | 18 | 69.6 | (25.17) | 18 | 78.2 | (31.36) |
| Change from Baseline to Day 8 | 18 | -38.9 | (13.13) | 18 | -37.9 | (23.12) |
| Change from Baseline to Day 15 | 18 | -37.6 | (16.17) | 17 | -37.1 | (31.52) |
| Change from Baseline to Day 22 | 18 | -36.3 | (22.79) | 17 | -43.0 | (30.51) |
| Change from Baseline to Day 29 | 17 | -41.5 | (19.75) | 18 | -36.6 | (37.18) |
| Change from Baseline to Last Visit | 18 | -38.1 | (24.05) | 18 | -36.6 | (37.18) |
| **Transferrin Saturation (%)** | | | | | | |
| Baseline | 18 | 35.6 | (14.72) | 18 | 37.3 | (11.39) |
| Change from Baseline to Day 8 | 18 | -0.2 | (27.82) | 18 | 5.4 | (31.47) |
| Change from Baseline to Day 15 | 18 | 12.6 | (41.69) | 17 | 18.1 | (34.06) |
| Change from Baseline to Day 22 | 18 | 6.2 | (26.30) | 17 | 8.6 | (28.04) |
| Change from Baseline to Day 29 | 17 | -17.0 | (15.56) | 18 | -1.4 | (19.86) |
| Change from Baseline to Last Visit | 18 | -15.7 | (16.12) | 18 | -1.4 | (19.86) |

FIG. 59

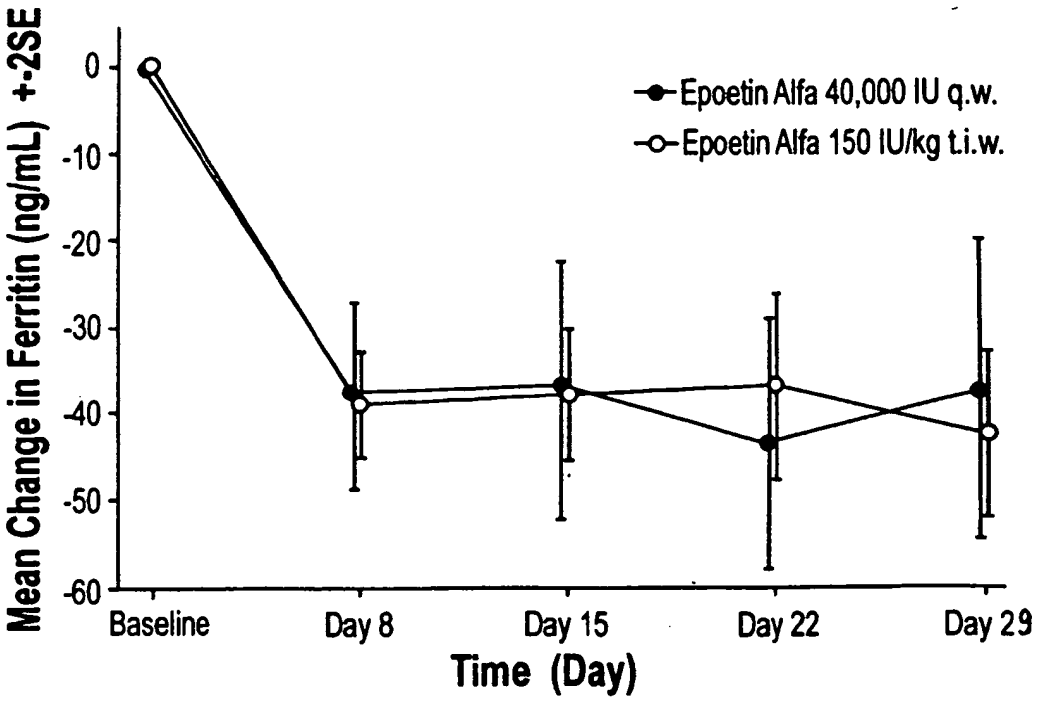

Mean Change in Ferritin (ng/mL) +-2SE
0
-10
-20
-30
-40
-50
-60
Baseline
Day 8
Day 15
Day 22
Day 29
Time (Day)
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 60

## SUBJECTS WITH HIGH BLOOD PRESSURE VALUES [a]

| SUBJECT | PRESTUDY | DAY 1 | DAY 8 | DAY 15 | DAY 22 | DAY 29 |
|---|---|---|---|---|---|---|
| **Epoetin Alfa 150 IU/kg t.i.w.** | | | | | | |
| 1005 | 119/69 | 129/72 | 119/62 | 140/87[b] | 127/70 | 121/72 |
| 2015 | 134/62 | 146/77[b] | 144/64[b] | 139/75 | 127/69 | 142/88[b] |

[a] As indicated by a systolic blood pressure ≥ 140 mmHg or a diastolic pressure ≥95 mmHg.

[b] Indicates a systolic blood pressure ≥ 140 mmHg.

FIG. 61

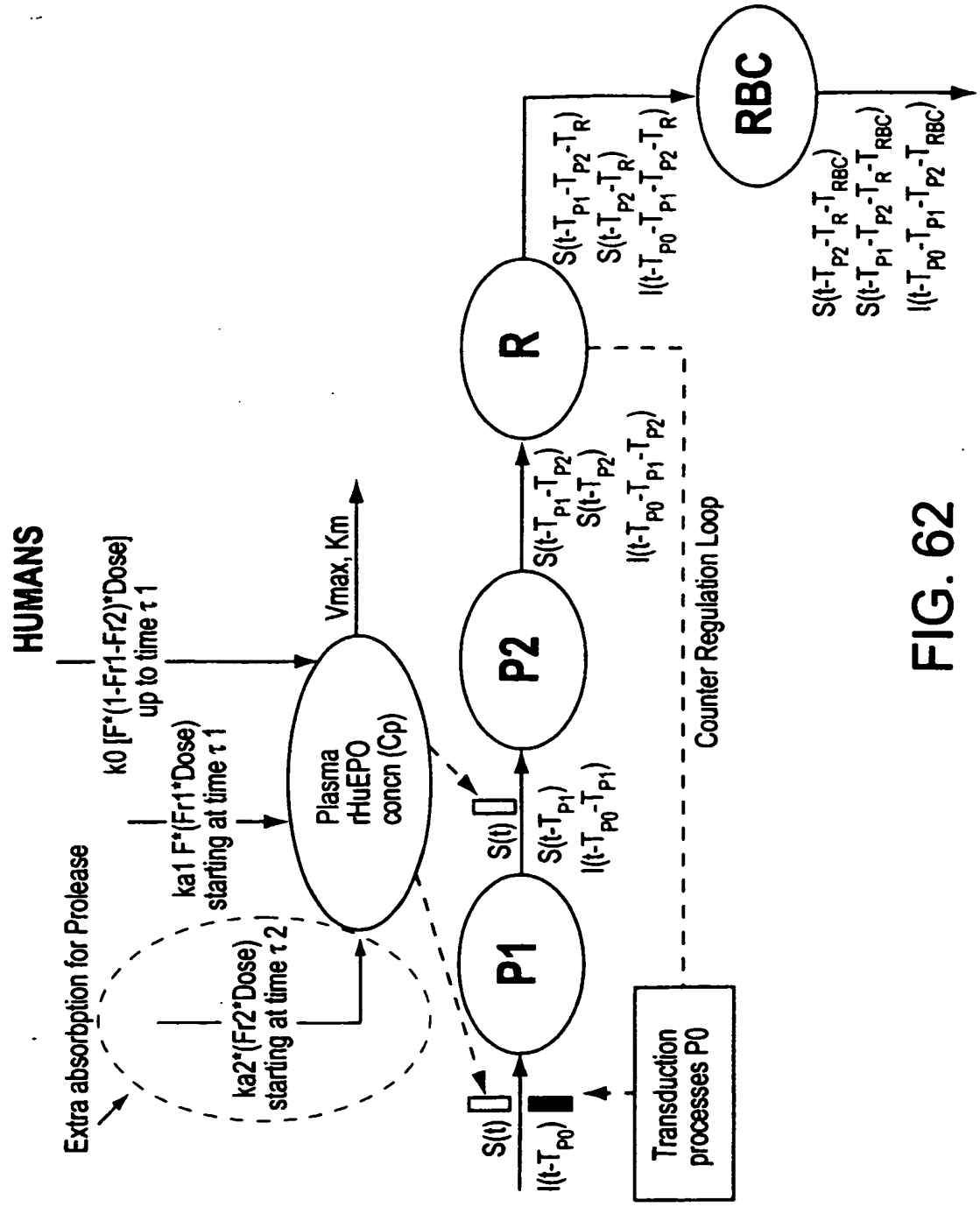

HUMANS
Extra absorption for Prolease
k0 [F*(1-Fr1-Fr2)*Dose] up to time τ 1
ka1 F*(Fr1*Dose) starting at time τ 1
ka2*(Fr2*Dose) starting at time τ 2
Plasma rHuEPO concn (Cp)
Vmax, Km
P1
P2
R
RBC
S(t)
I(t-T_P0)
S(t-T_P1)
I(t-T_P0-T_P1)
S(t-T_P1-T_P2)
S(t-T_P2)
I(t-T_P0-T_P1-T_P2)
S(t-T_P1-T_P2-T_R)
S(t-T_P2-T_R)
I(t-T_P0-T_P1-T_P2-T_R)
S(t-T_P2-T_R-T_RBC)
S(t-T_P1-T_P2-T_R-T_RBC)
I(t-T_P0-T_P1-T_P2-T_RBC)
Transduction processes P0
Counter Regulation Loop

FIG. 62

# PHARMACOKINETIC PARAMETERS AFTER rHuEpo DOSING

| | EPREX *single dose* | PROLEASE |
|---|---|---|
| ka1 ($hr^{-1}$) | 0.0219 | 0.0084 |
| ka2 ($hr^{-1}$) | - | 0.0027 |
| fr1 | 0.1308 | 0.3643 |
| fr2 | - | 0.0782 |
| kel ($hr^{-1}$) | - | 0.0027 |
| Vmax (IU/kg/hr) | 138.5 | - |
| Km (IU/L) | 20940 | - |
| Vd (L/kg) | 0.0558 | 0.2072 |
| Tau1 (hr) | 44 | 45.18 |
| Tau2 (hr) | - | 215.2 |
| F=0.3884+0.00024952*DOSE | | |

| For EPREX *150 IU/kg/t.i.w* | *600 IU/kg/wk* |
|---|---|
| 0.1193 | - |
| 10 | 32.15 |
| F=0.25 | |

FIG. 63

# PHARMACODYNAMIC PARAMETERS AFTER rHuEpo DOSING

## PHYSIOLOGICAL/LIFESPAN PARAMETERS ESTIMATED FROM SINGLE DOSE DATA

| | |
|---|---|
| TP1 | 88.17 |
| TP2 | 10.76 |
| *RL | 116.6 |
| **IC50 | 38.71 |
| TPO | 137.5 |

**EPREX**

| single dose | multiple dosing | |
|---|---|---|
| * (males) | males | females |
| ** 4.251 | 8.186 | 4.178 |
| 26.53 | 61.15 | 57.3 |

FIG. 64

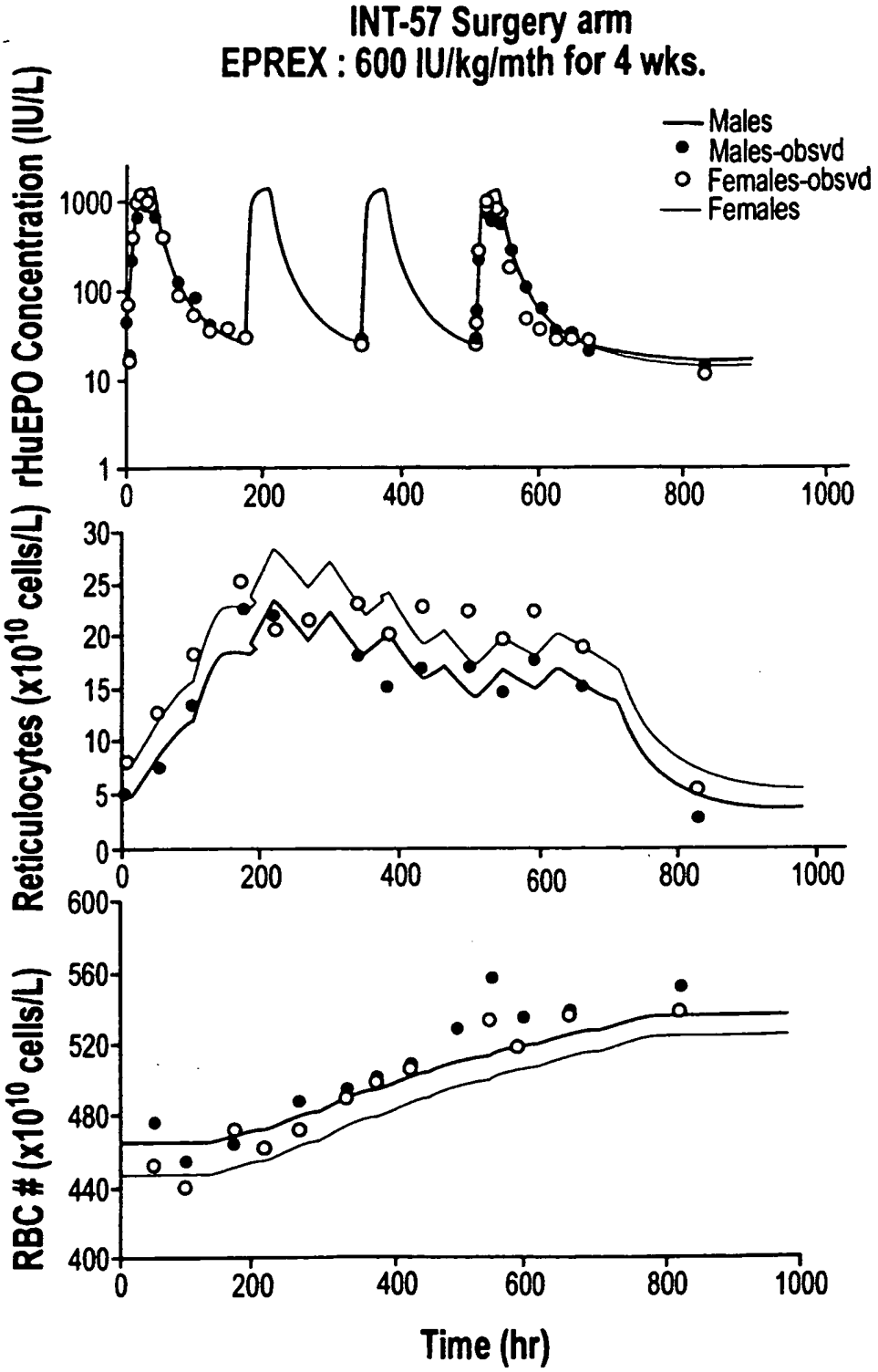

INT-57 Surgery arm
EPREX : 600 IU/kg/mth for 4 wks.
Males
Males-obsvd
Females-obsvd
Females
rHuEPO Concentration (IU/L)
1000
100
10
1
0
200
400
600
800
1000
Reticulocytes (x10^10 cells/L)
30
25
20
15
10
5
0
RBC # (x10^10 cells/L)
600
560
520
480
440
400
Time (hr)

FIG. 65

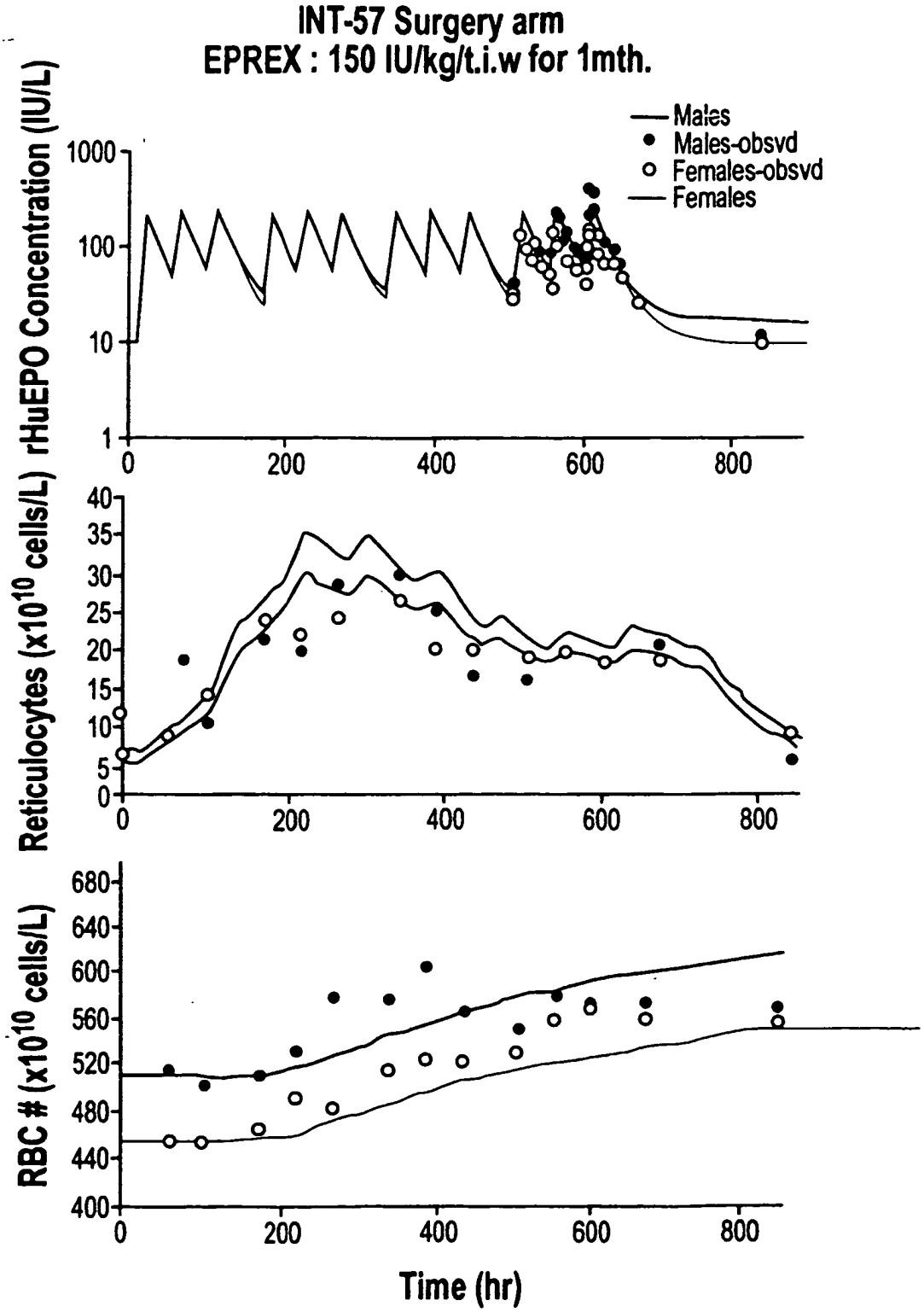

INT-57 Surgery arm
EPREX : 150 IU/kg/t.i.w for 1mth.
Males
Males-obsvd
Females-obsvd
Females
rHuEPO Concentration (IU/L)
1000
100
10
1
0
200
400
600
800
Reticulocytes (x10^10 cells/L)
40
35
30
25
20
15
10
5
0
RBC # (x10^10 cells/L)
680
640
600
560
520
480
440
400
Time (hr)

FIG. 66

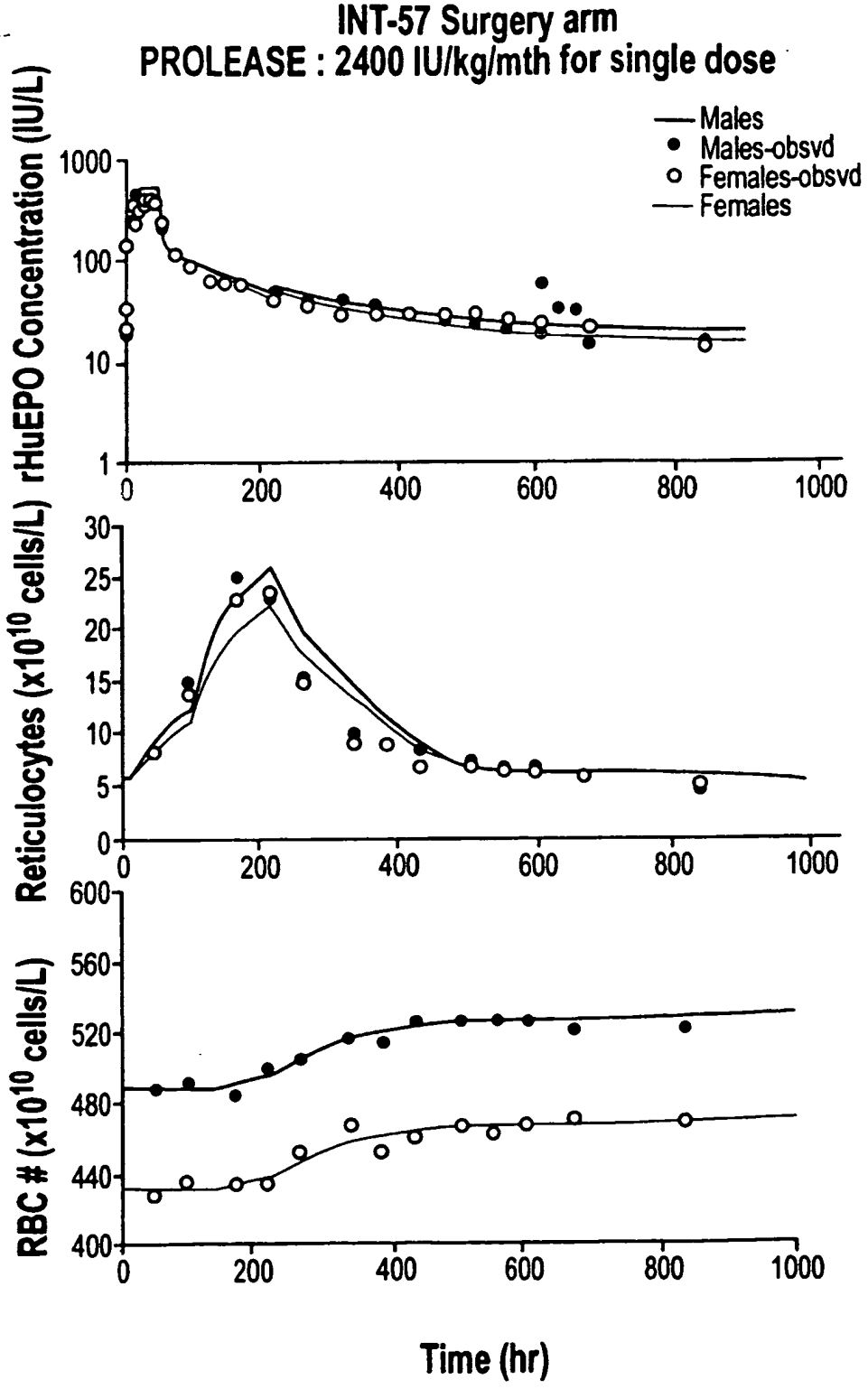

INT-57 Surgery arm
PROLEASE : 2400 IU/kg/mth for single dose
Males
Males-obsvd
Females-obsvd
Females
rHuEPO Concentration (IU/L)
1000
100
10
1
0
200
400
600
800
1000
Reticulocytes (x10^10 cells/L)
30
25
20
15
10
5
0
RBC # (x10^10 cells/L)
600
560
520
480
440
400
Time (hr)

FIG. 67

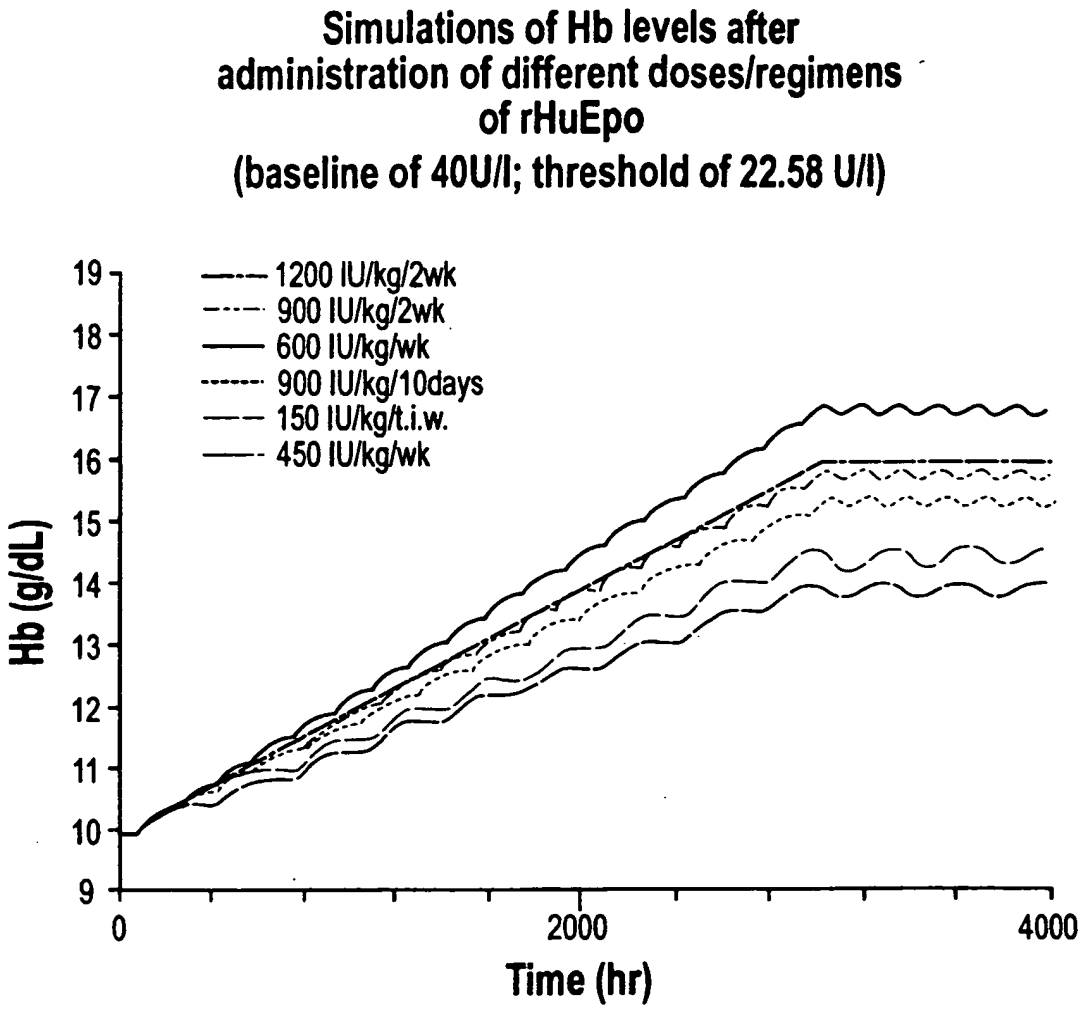

Simulations of Hb levels after
administration of different doses/regimens
of rHuEpo
(baseline of 40U/l; threshold of 22.58 U/l)
1200 IU/kg/2wk
900 IU/kg/2wk
600 IU/kg/wk
900 IU/kg/10days
150 IU/kg/t.i.w.
450 IU/kg/wk
Hb (g/dL)
19
18
17
16
15
14
13
12
11
10
9
0
2000
4000
Time (hr)

FIG.68

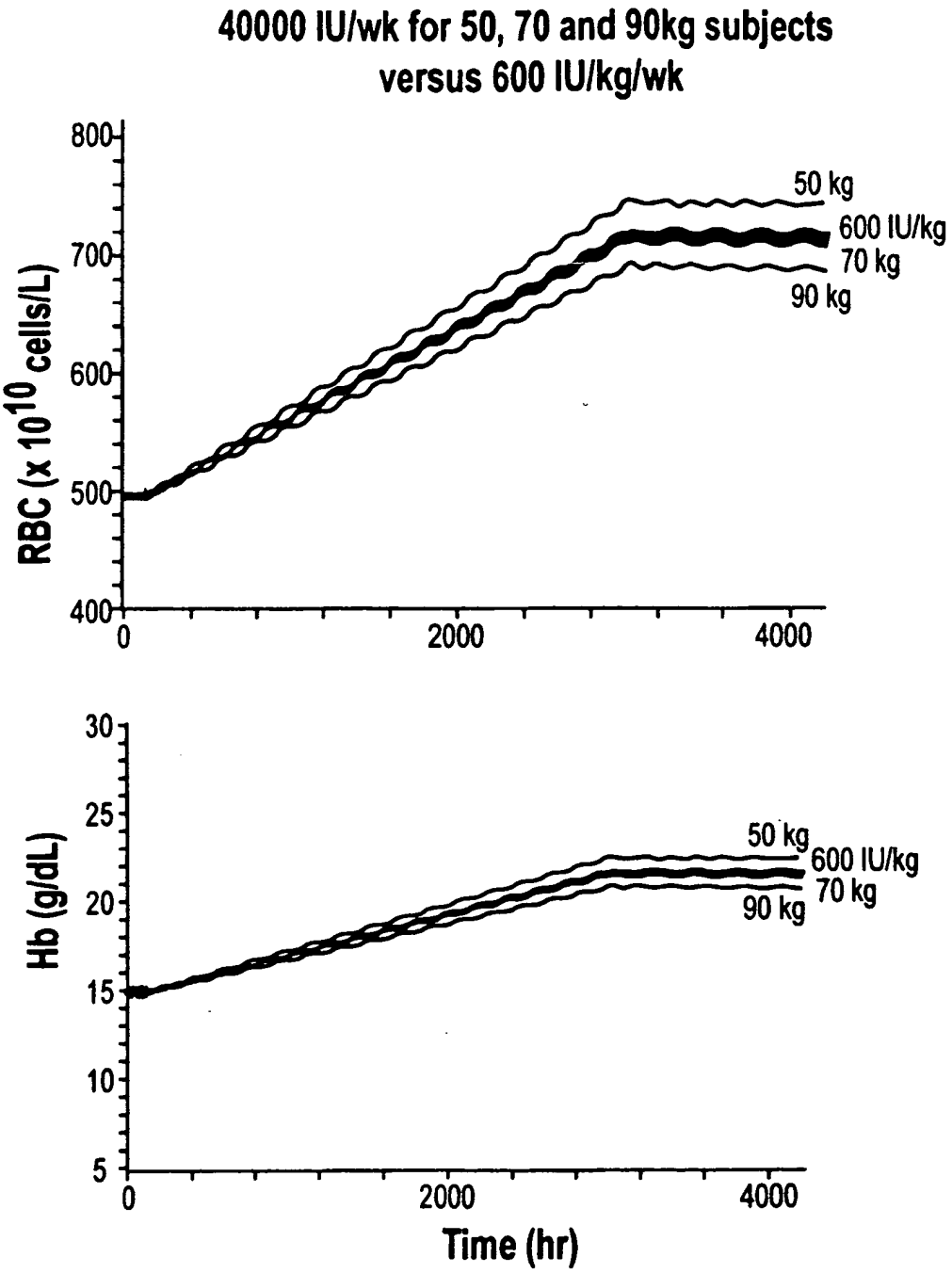

40000 IU/wk for 50, 70 and 90kg subjects
versus 600 IU/kg/wk
RBC (x 10^10 cells/L)
800
700
600
500
400
0
2000
4000
50 kg
600 IU/kg
70 kg
90 kg
Hb (g/dL)
30
25
20
15
10
5
0
2000
4000
50 kg
600 IU/kg
70 kg
90 kg
Time (hr)

FIG.69

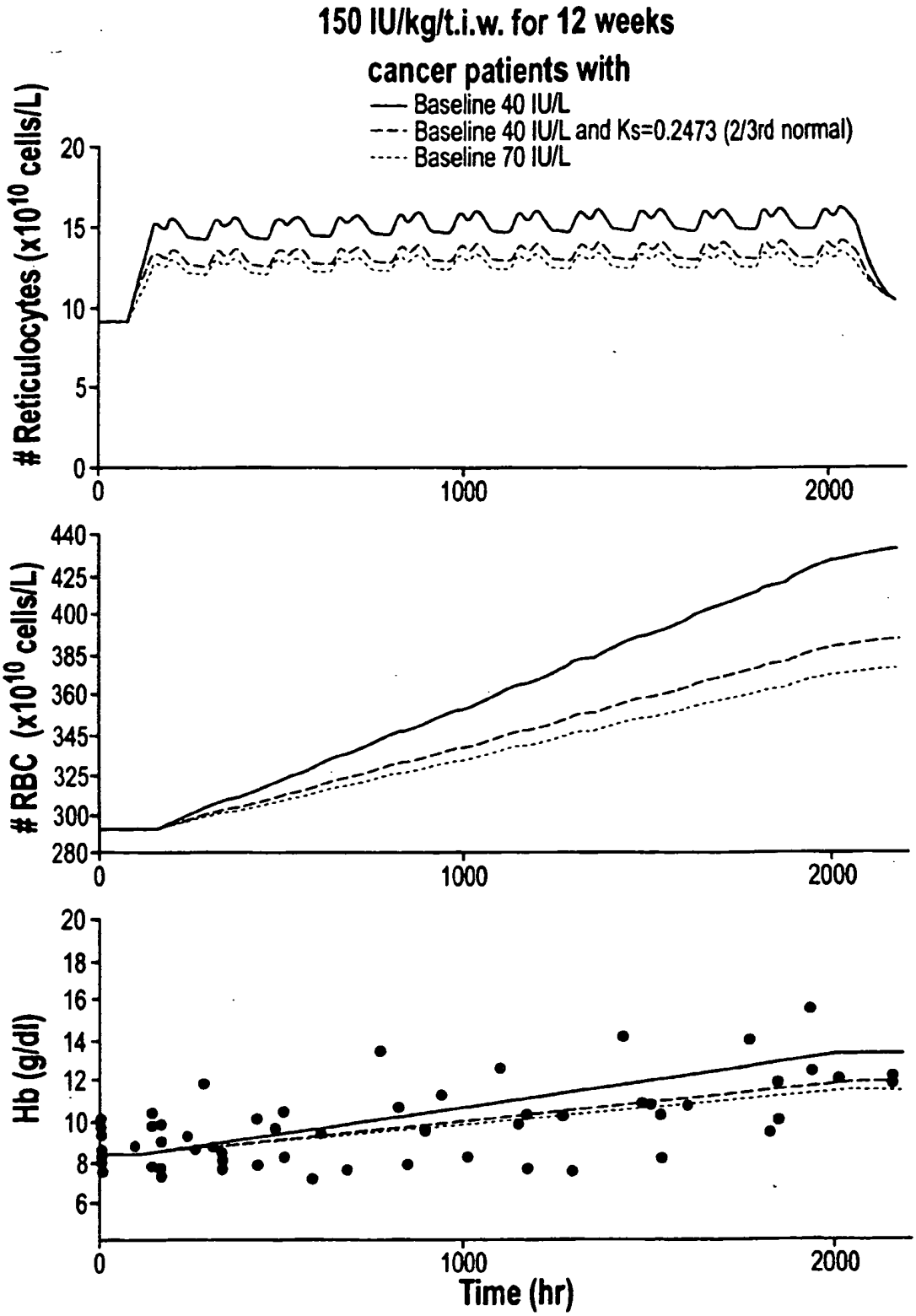

150 IU/kg/t.i.w. for 12 weeks
cancer patients with
Baseline 40 IU/L
Baseline 40 IU/L and Ks=0.2473 (2/3rd normal)
Baseline 70 IU/L
# Reticulocytes (x10^10 cells/L)
20
15
10
5
0
0
1000
2000
# RBC (x10^10 cells/L)
440
425
400
385
360
345
325
300
280
0
1000
2000
Hb (g/dl)
20
18
16
14
12
10
8
6
0
1000
2000
Time (hr)

FIG. 70A

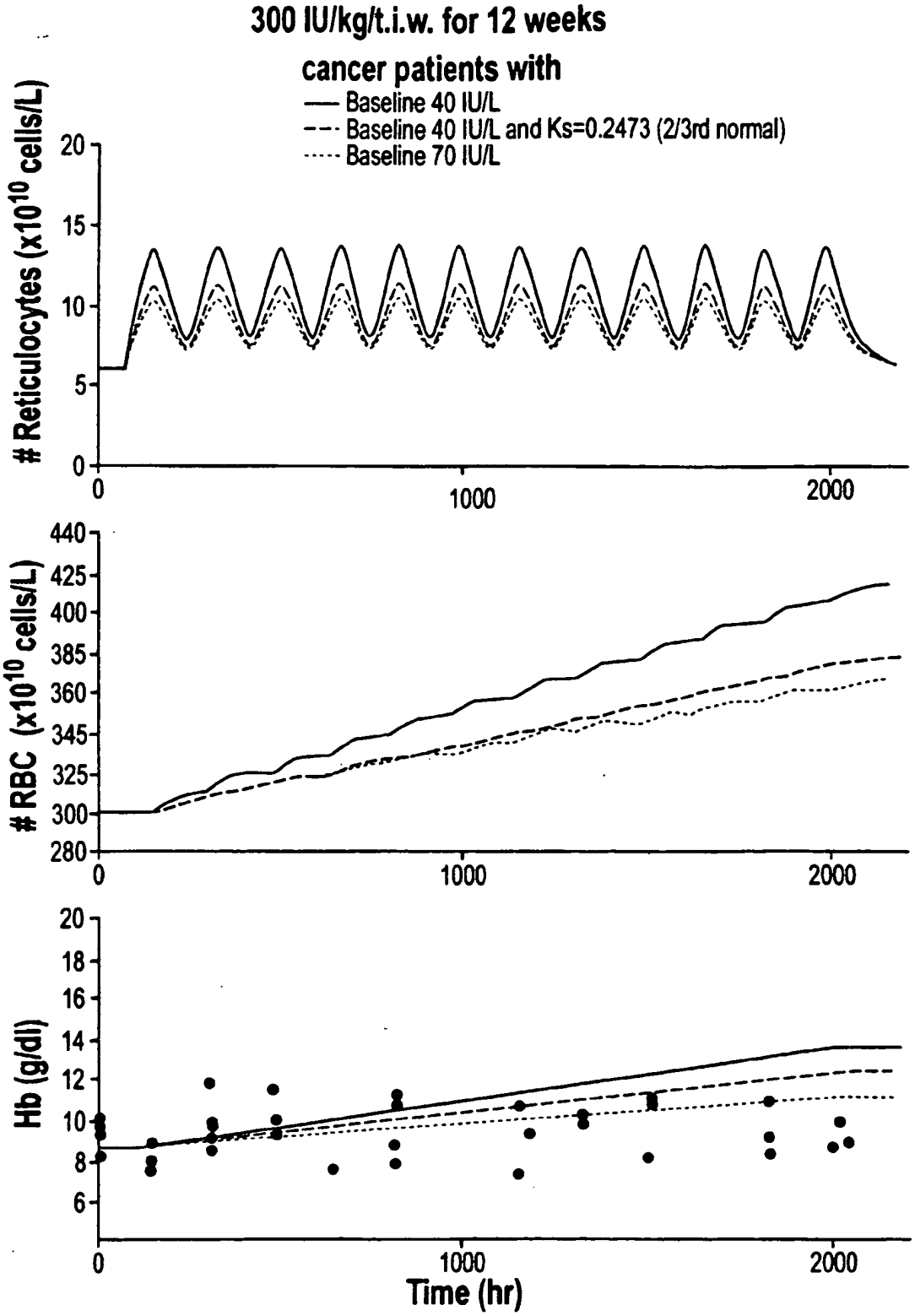

300 IU/kg/t.i.w. for 12 weeks
cancer patients with
Baseline 40 IU/L
Baseline 40 IU/L and Ks=0.2473 (2/3rd normal)
Baseline 70 IU/L
# Reticulocytes (x10^10 cells/L)
20
15
10
5
0
0
1000
2000
# RBC (x10^10 cells/L)
440
425
400
385
360
345
325
300
280
0
1000
2000
Hb (g/dl)
20
18
16
14
12
10
8
6
0
1000
2000
Time (hr)

FIG. 70B

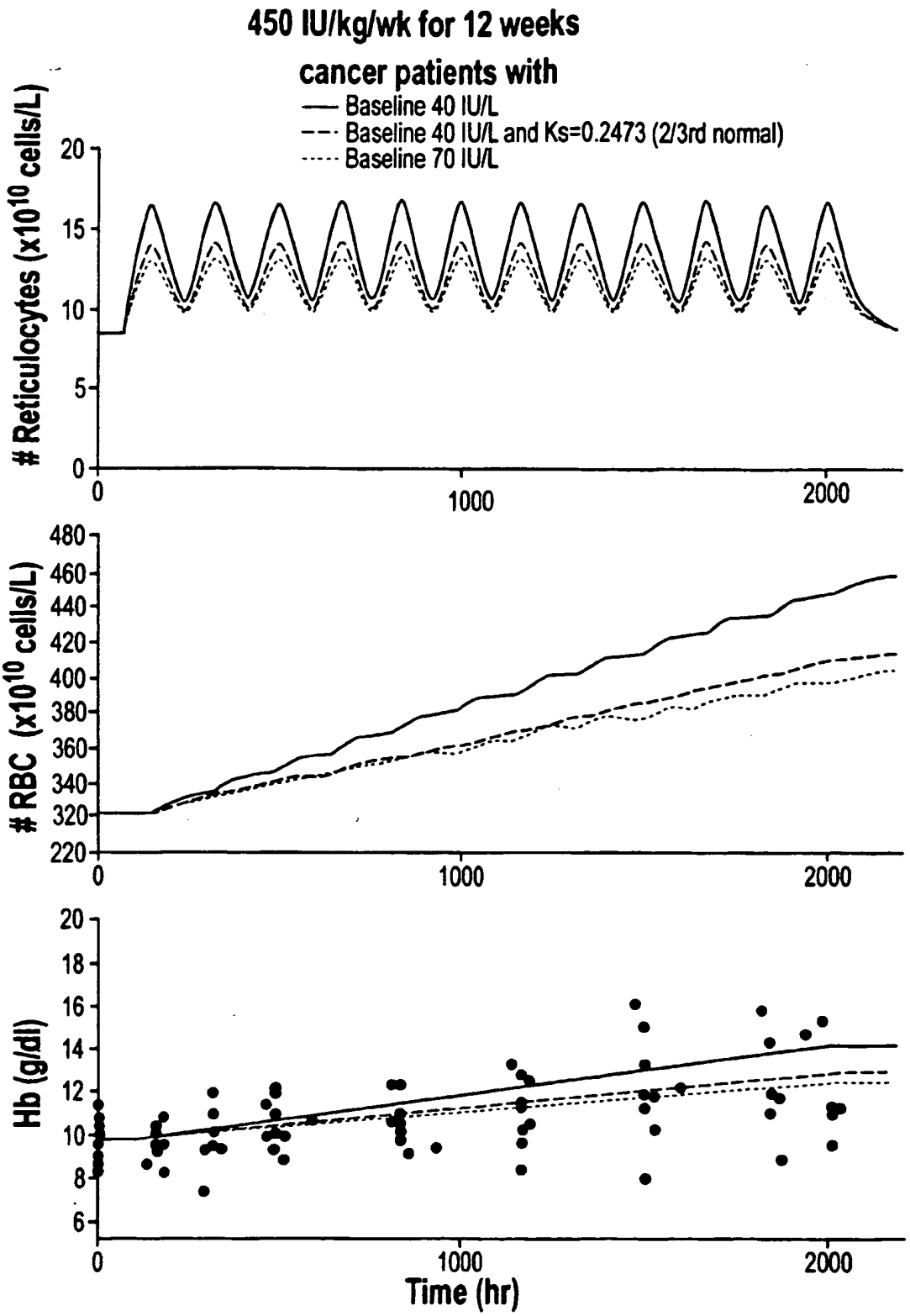

450 IU/kg/wk for 12 weeks
cancer patients with
Baseline 40 IU/L
Baseline 40 IU/L and Ks=0.2473 (2/3rd normal)
Baseline 70 IU/L
# Reticulocytes (x10^10 cells/L)
20
15
10
5
0
0
1000
2000
# RBC (x10^10 cells/L)
480
460
440
420
400
380
360
340
320
220
0
1000
2000
Hb (g/dl)
20
18
16
14
12
10
8
6
0
1000
2000
Time (hr)

FIG. 70C

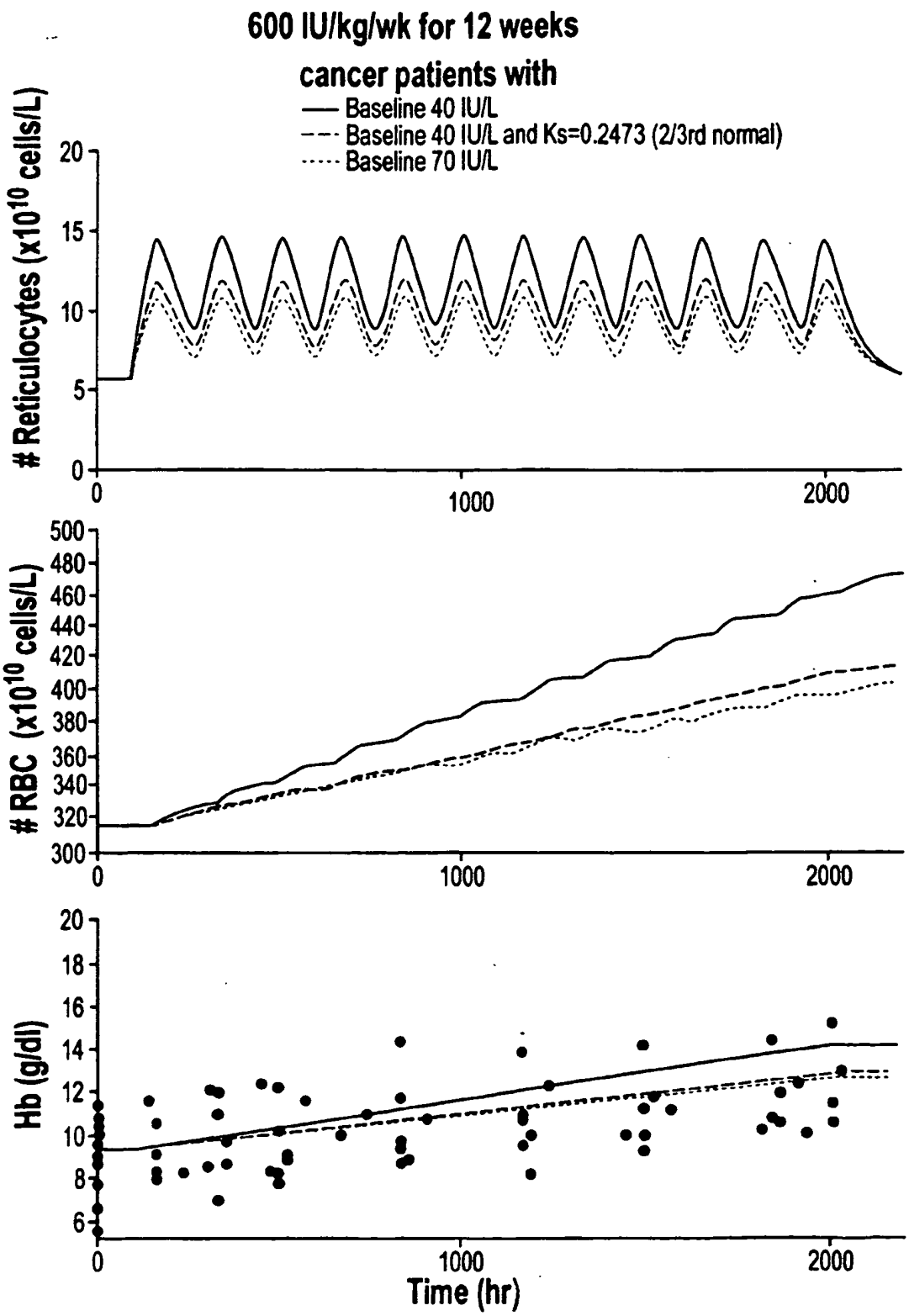

600 IU/kg/wk for 12 weeks
cancer patients with
Baseline 40 IU/L
Baseline 40 IU/L and Ks=0.2473 (2/3rd normal)
Baseline 70 IU/L
# Reticulocytes (x10^10 cells/L)
20
15
10
5
0
0
1000
2000
# RBC (x10^10 cells/L)
500
480
460
440
420
400
380
360
340
320
300
0
1000
2000
Hb (g/dl)
20
18
16
14
12
10
8
6
0
1000
2000
Time (hr)

FIG. 70D

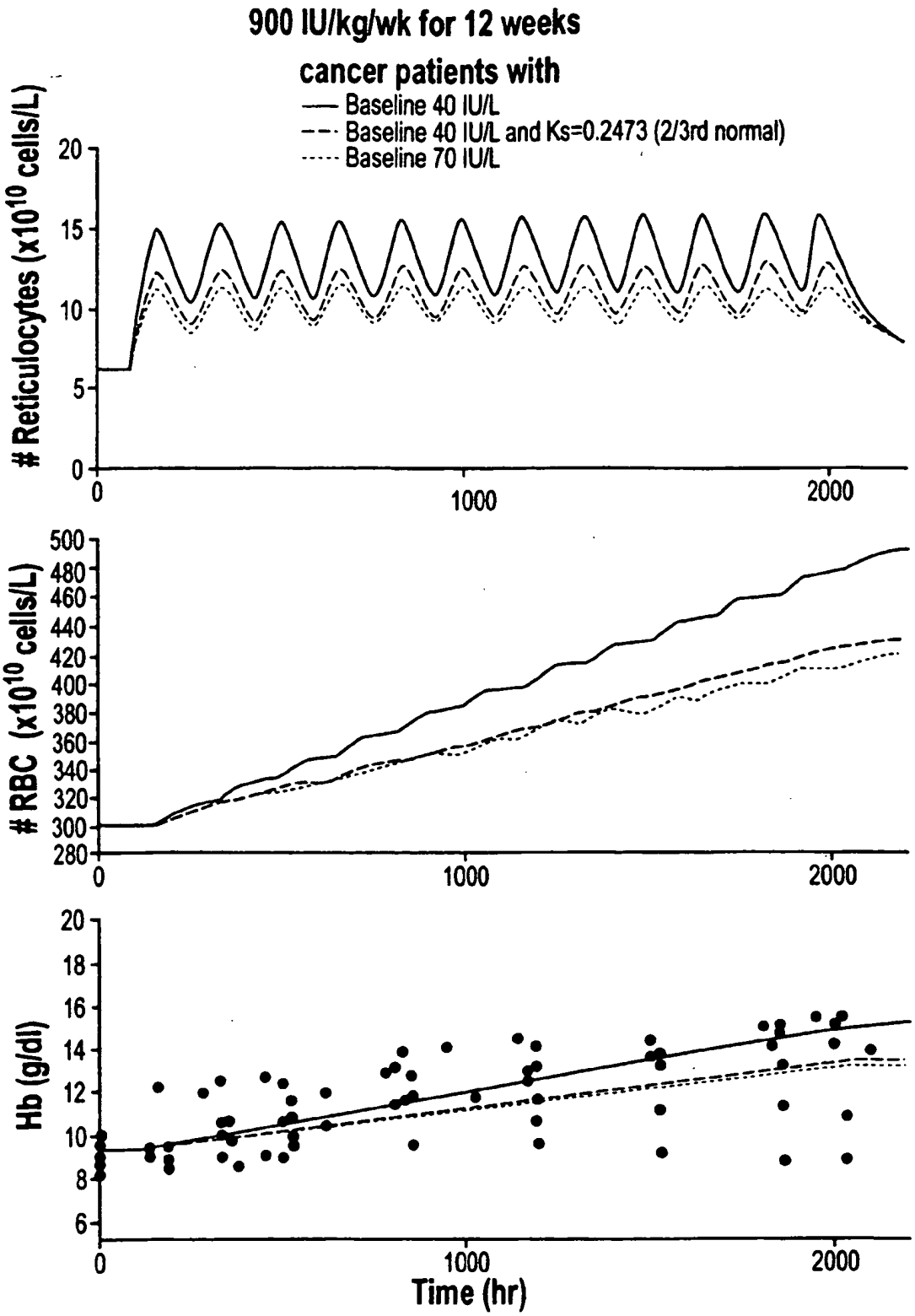

900 IU/kg/wk for 12 weeks
cancer patients with
Baseline 40 IU/L
Baseline 40 IU/L and Ks=0.2473 (2/3rd normal)
Baseline 70 IU/L
# Reticulocytes (x10^10 cells/L)
20
15
10
5
0
0
1000
2000
# RBC (x10^10 cells/L)
500
480
460
440
420
400
380
360
340
320
300
280
0
1000
2000
Hb (g/dl)
20
18
16
14
12
10
8
6
0
1000
2000
Time (hr)

FIG. 70E

**DM00004**
**Mean Hemoglobin Time-Concentration Profiles**

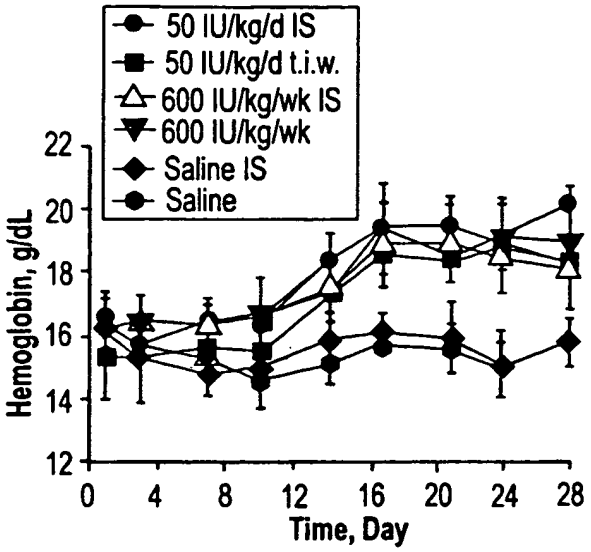



FIG. 71

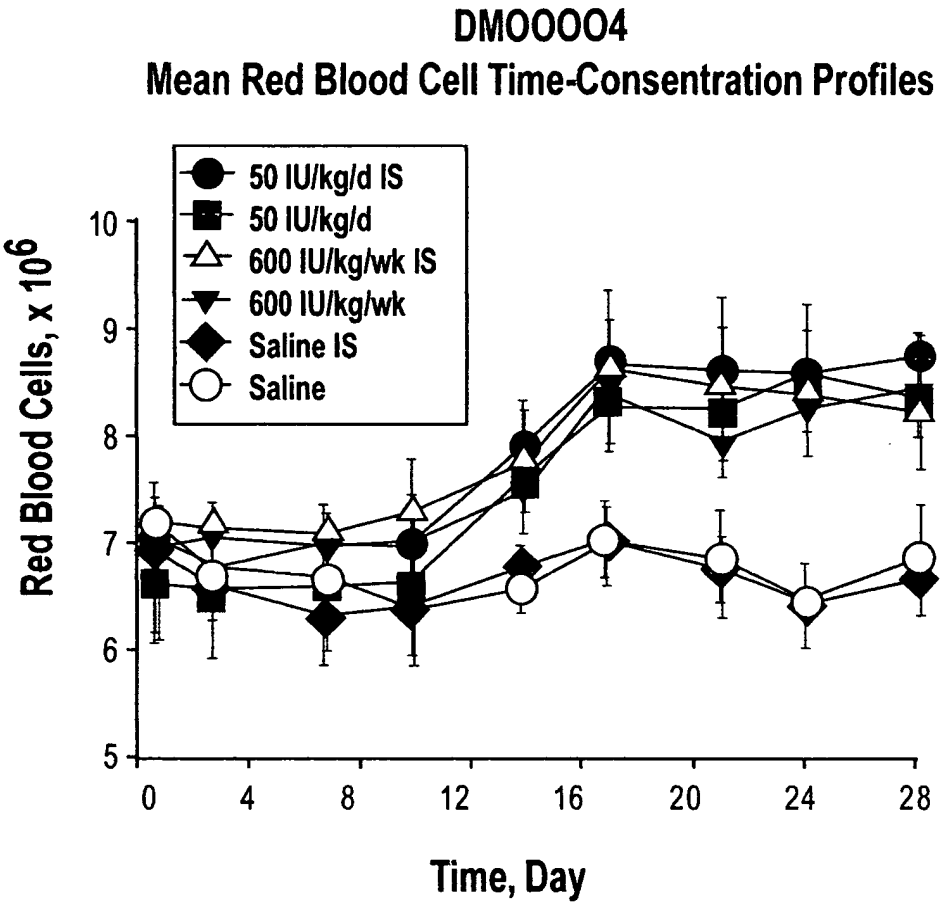

DMOOOO4
Mean Red Blood Cell Time-Consentration Profiles
50 IU/kg/d IS
50 IU/kg/d
600 IU/kg/wk IS
600 IU/kg/wk
Saline IS
Saline
Red Blood Cells, x 10^6
10
9
8
7
6
5
0
4
8
12
16
20
24
28
Time, Day

FIG.72

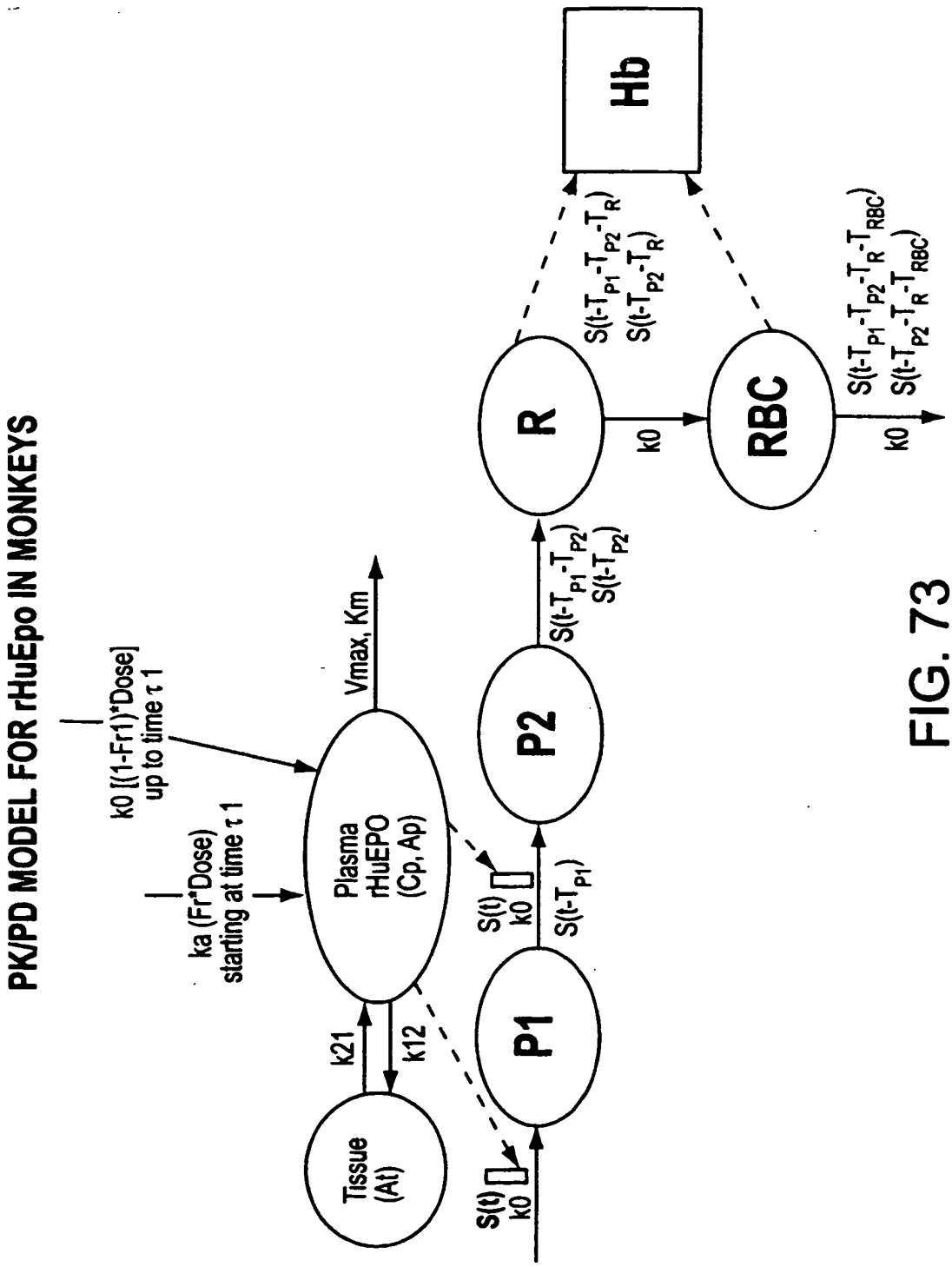

PK/PD MODEL FOR rHuEpo IN MONKEYS
k0 [(1-Fr1)*Dose] up to time τ 1
ka (Fr*Dose) starting at time τ 1
Plasma rHuEPO (Cp, Ap)
Vmax, Km
Tissue (At)
k21
k12
P1
P2
R
RBC
Hb
k0
S(t)
S(t-T_P1)
S(t-T_P1-T_P2)
S(t-T_P2)
S(t-T_P1-T_P2-T_R)
S(t-T_P2-T_R)
S(t-T_P1-T_P2-T_R-T_RBC)
S(t-T_P2-T_R-T_RBC)

FIG. 73

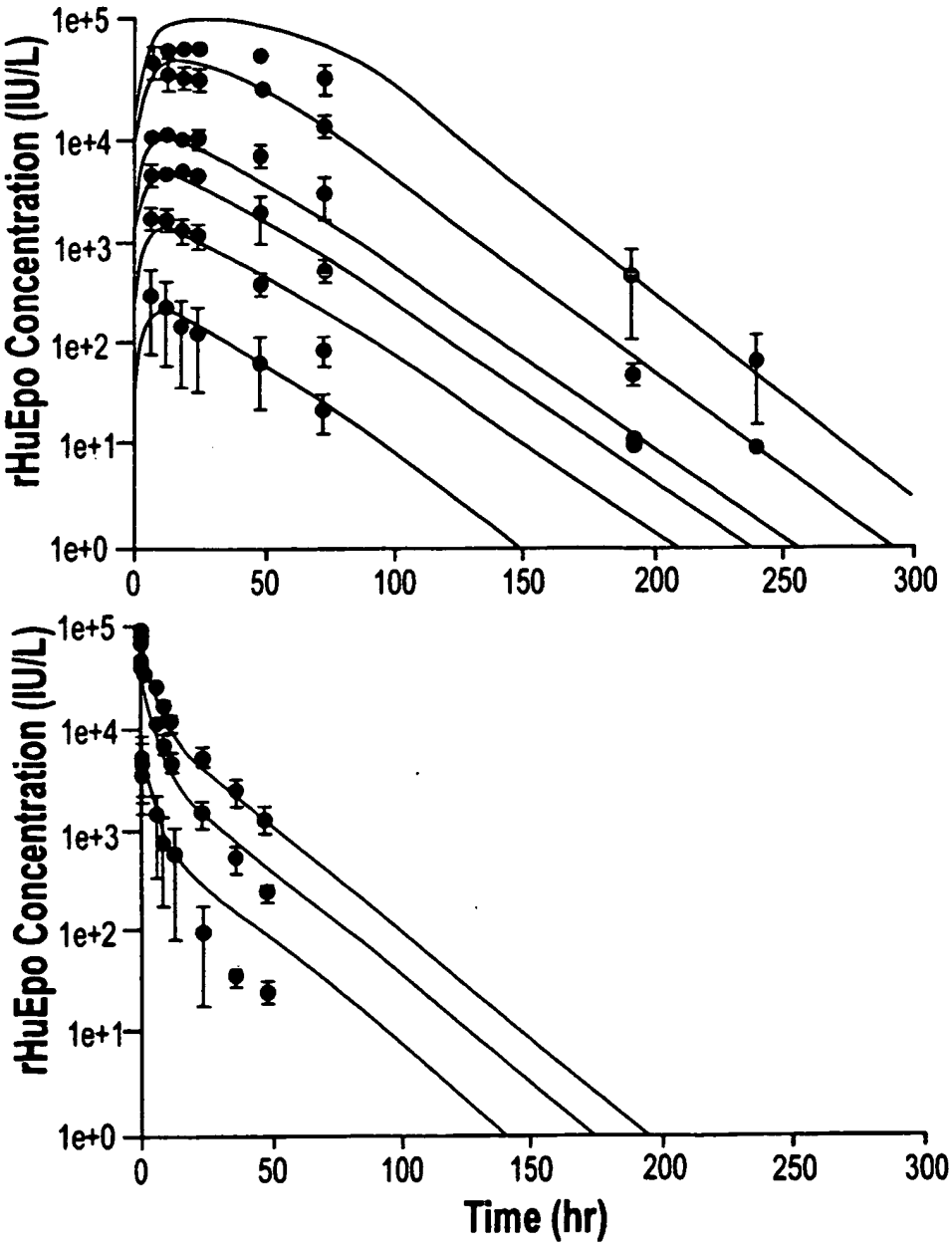

rHuEpo Concentration (IU/L)
1e+5
1e+4
1e+3
1e+2
1e+1
1e+0
0
50
100
150
200
250
300
rHuEpo Concentration (IU/L)
1e+5
1e+4
1e+3
1e+2
1e+1
1e+0
0
50
100
150
200
250
300
Time (hr)

FIG. 74

# PHARMACOKINETIC PARAMETERS IN MONKEYS

| | EPREX |
|---|---|
| Vmax (IU/kg/hr) | 480.3 |
| Km (IU/L) | 35190 |
| Vd (L/kg) | 0.05689 |
| k12 (hr-1) | 0.1192 |
| k21 (hr-1) | 0.07916 |
| Tau (hr) | 10 |
| ka (hr-1) | 0.04427 |
| ka (hr-1)-lowest dose | 0.05255 |
| Fr | 0.6452 |
| F (400 IU/kg dose) | 0.2666 |
| F (1000 IU/kg dose) | 0.7348 |
| F (higher doses) | 1 |

FIG. 75

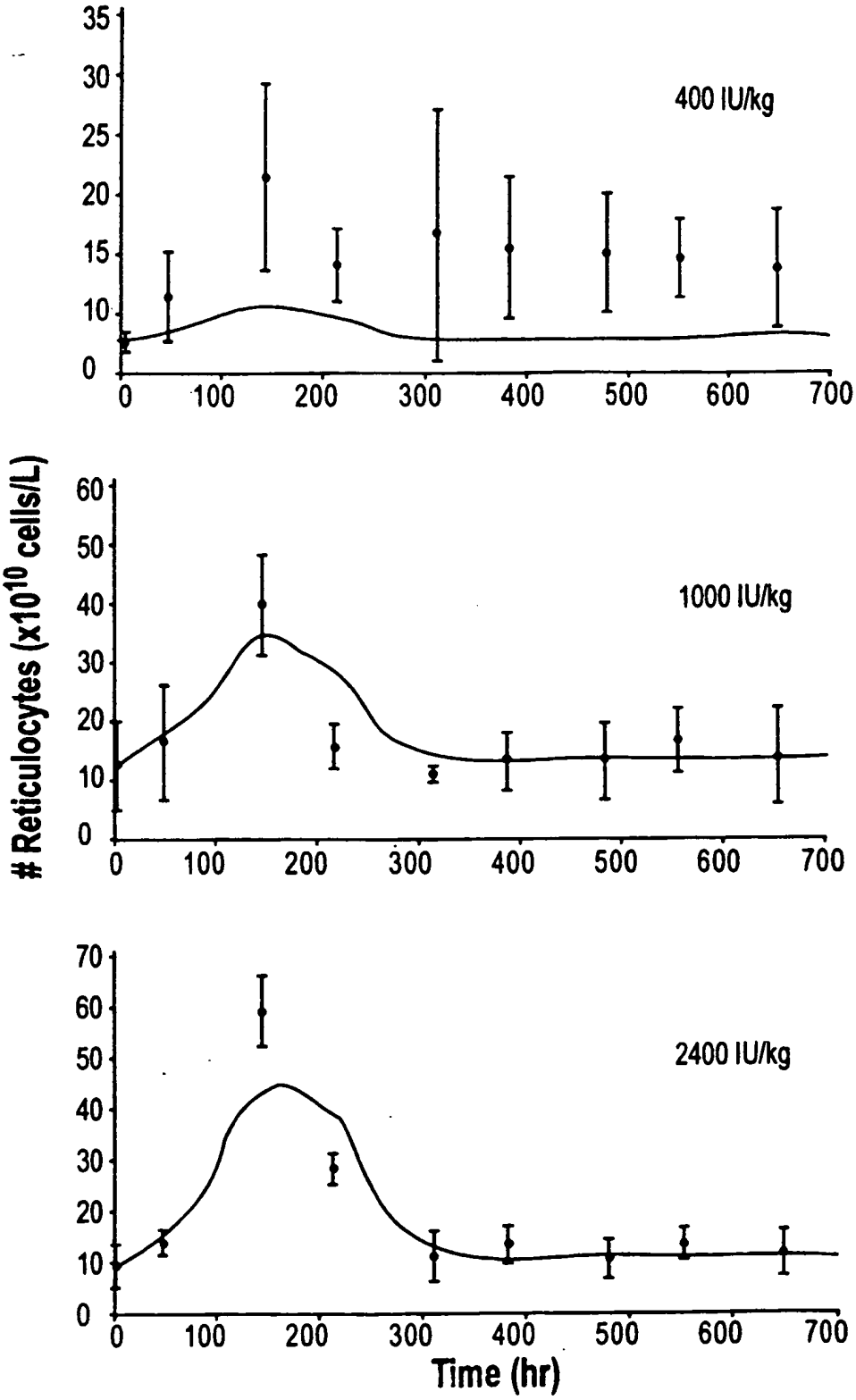

400 IU/kg
1000 IU/kg
2400 IU/kg
# Reticulocytes (x10^10 cells/L)
Time (hr)
0
100
200
300
400
500
600
700

FIG. 76A

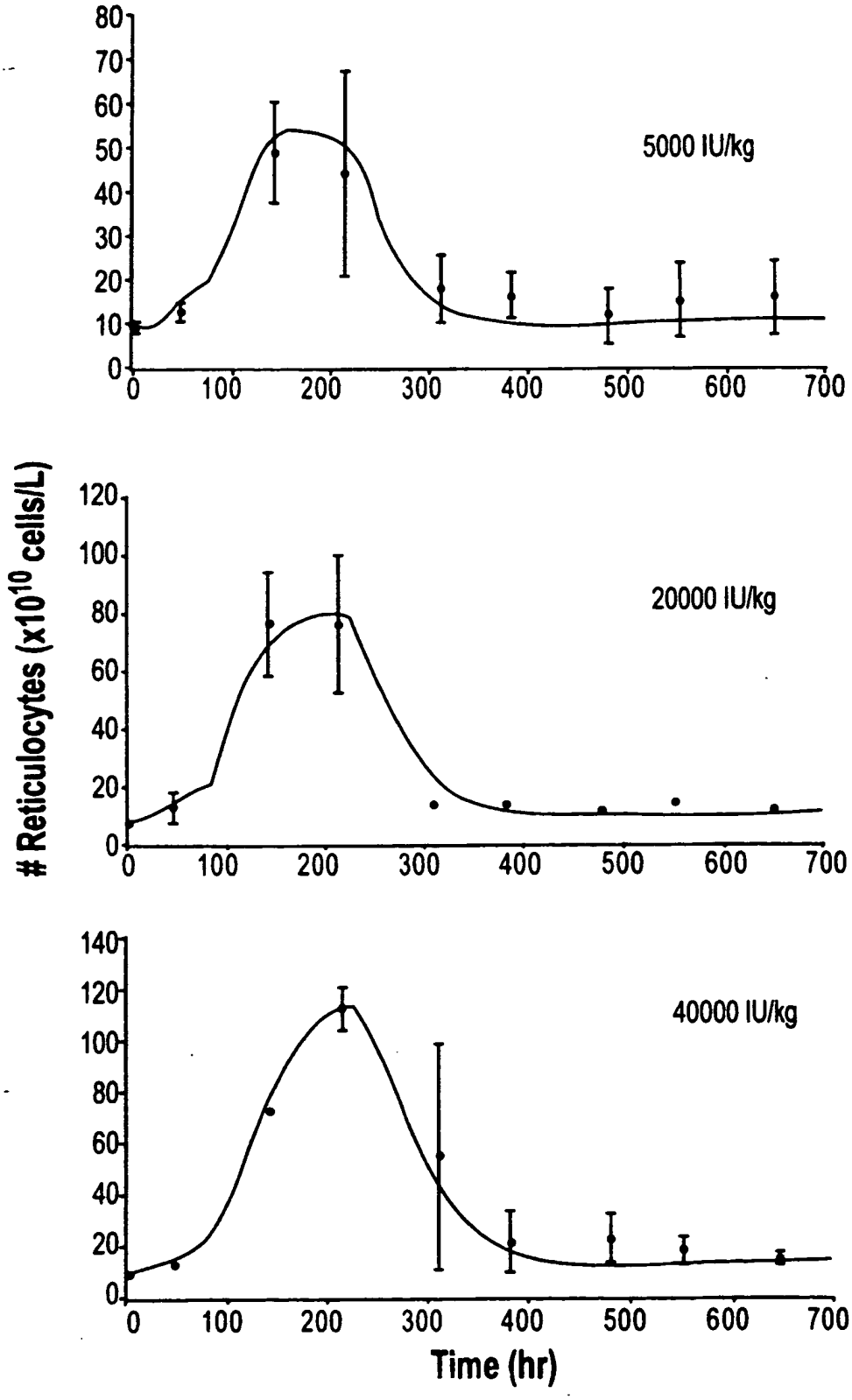

5000 IU/kg
20000 IU/kg
40000 IU/kg
# Reticulocytes (x10^10 cells/L)
Time (hr)
0
100
200
300
400
500
600
700

FIG. 76B

## PHARMACODYNAMIC PARAMETERS IN MONKEYS

| | EPREX |
|---|---|
| TP1 (h) | 70.38 |
| TP2 (h) | 14.95 |
| RL (h) | 141.6 |
| Smax | 3.133 |
| SC50 (IU/L) | 842.5 |

FIG. 77

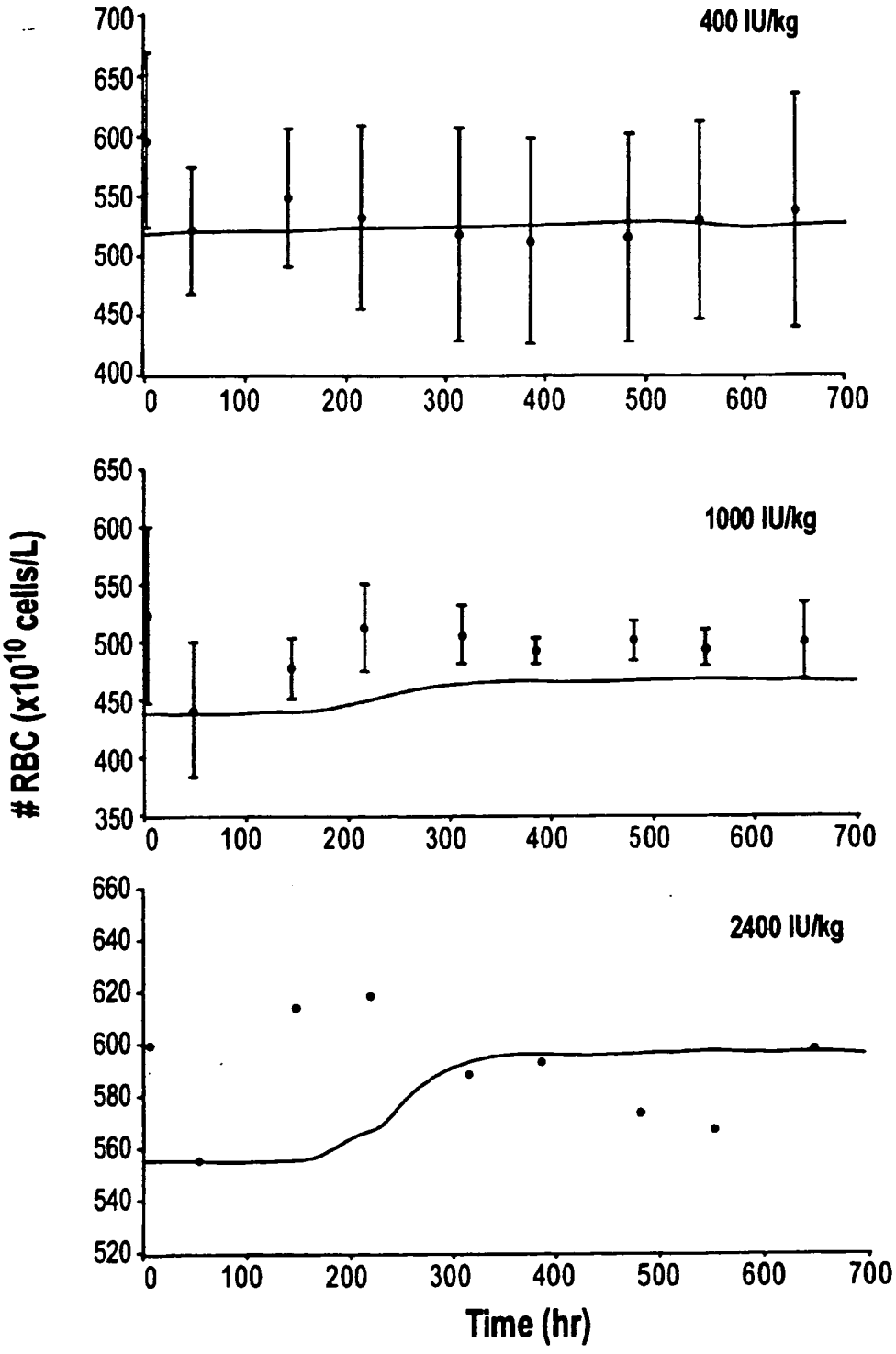



FIG. 78A

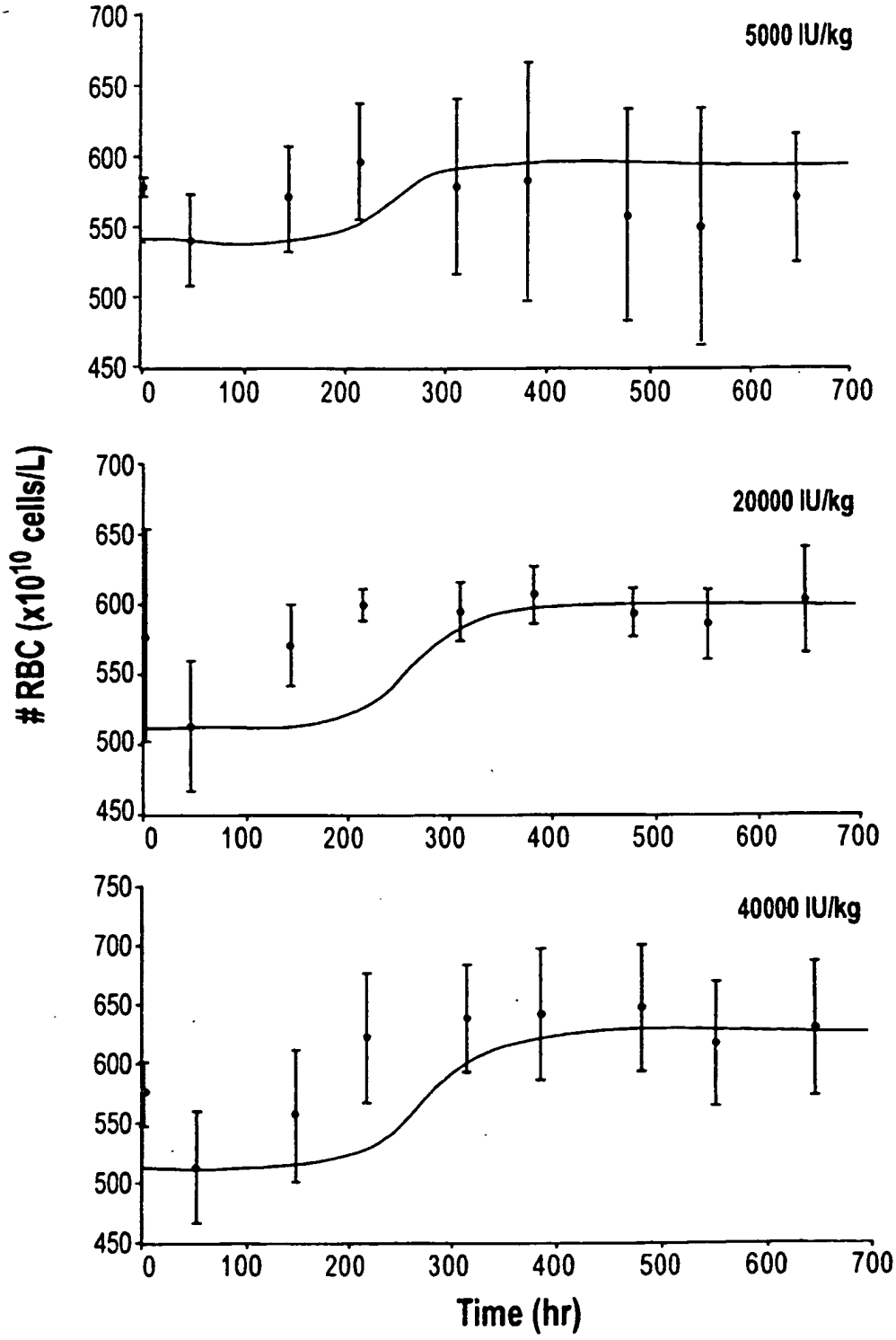

5000 IU/kg
20000 IU/kg
40000 IU/kg
# RBC (x10^10 cells/L)
Time (hr)
700
650
600
550
500
450
750
0
100
200
300
400
500
600
700

FIG. 78B

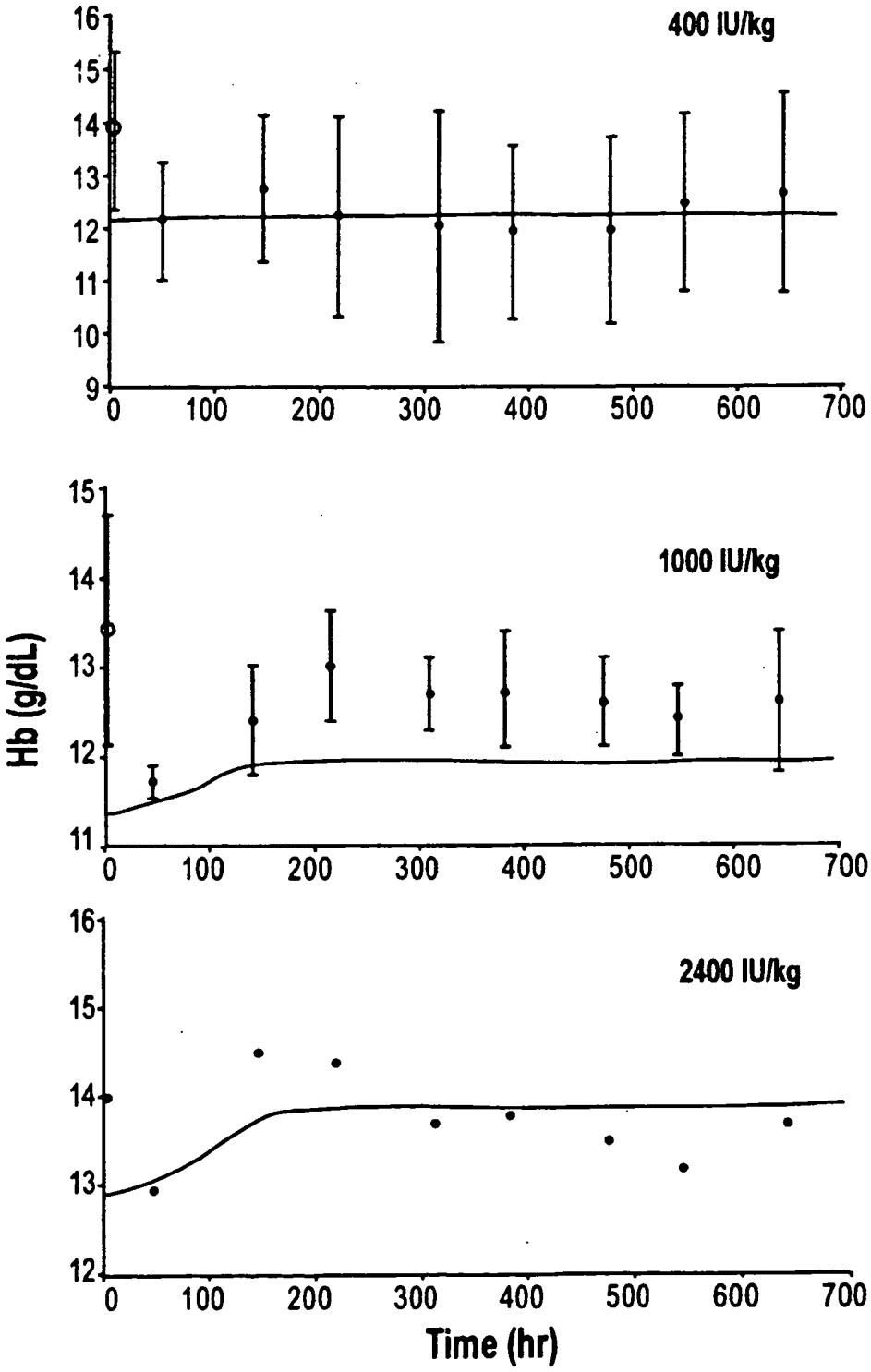

400 IU/kg
1000 IU/kg
2400 IU/kg
Hb (g/dL)
Time (hr)
16
15
14
13
12
11
10
9
0
100
200
300
400
500
600
700

FIG. 79A

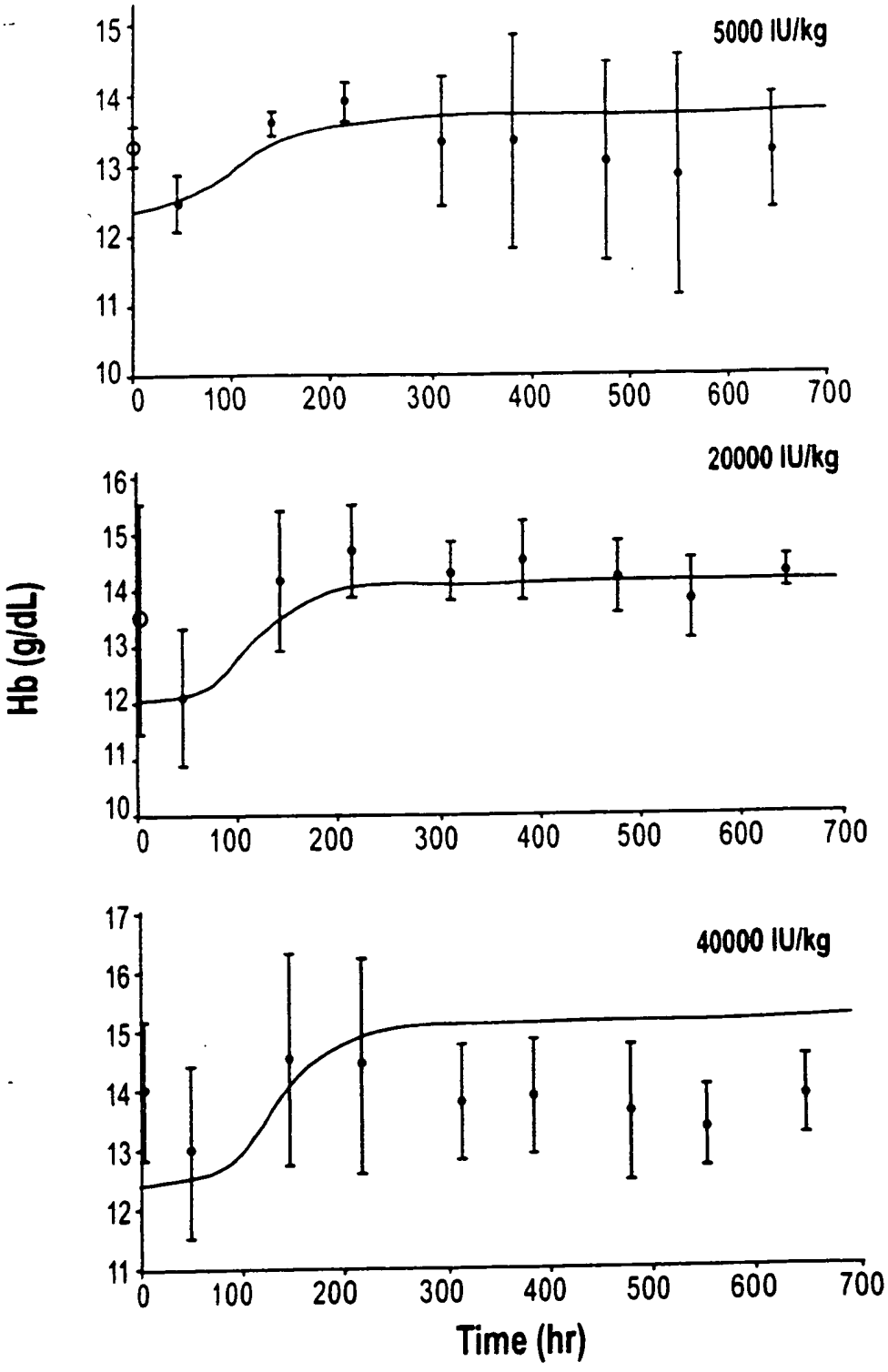

5000 IU/kg
20000 IU/kg
40000 IU/kg
Hb (g/dL)
Time (hr)
15
14
13
12
11
10
16
17
0
100
200
300
400
500
600
700

FIG. 79B

## PHARMACODYNAMIC PARAMETERS IN HUMANS

| | EPREX |
|---|---|
| TP1 (h) | 88.17 |
| TP2 (h) | 10.76 |
| RL (h) | 116.6 |
| Smax | 4.251 |
| SC50 (IU/L) | 26.53 |
| TP0 (h) | 137.5 |
| $IC_{50}$ ($x10^{10}$ Reti/L) | 38.71 |

FIG. 80

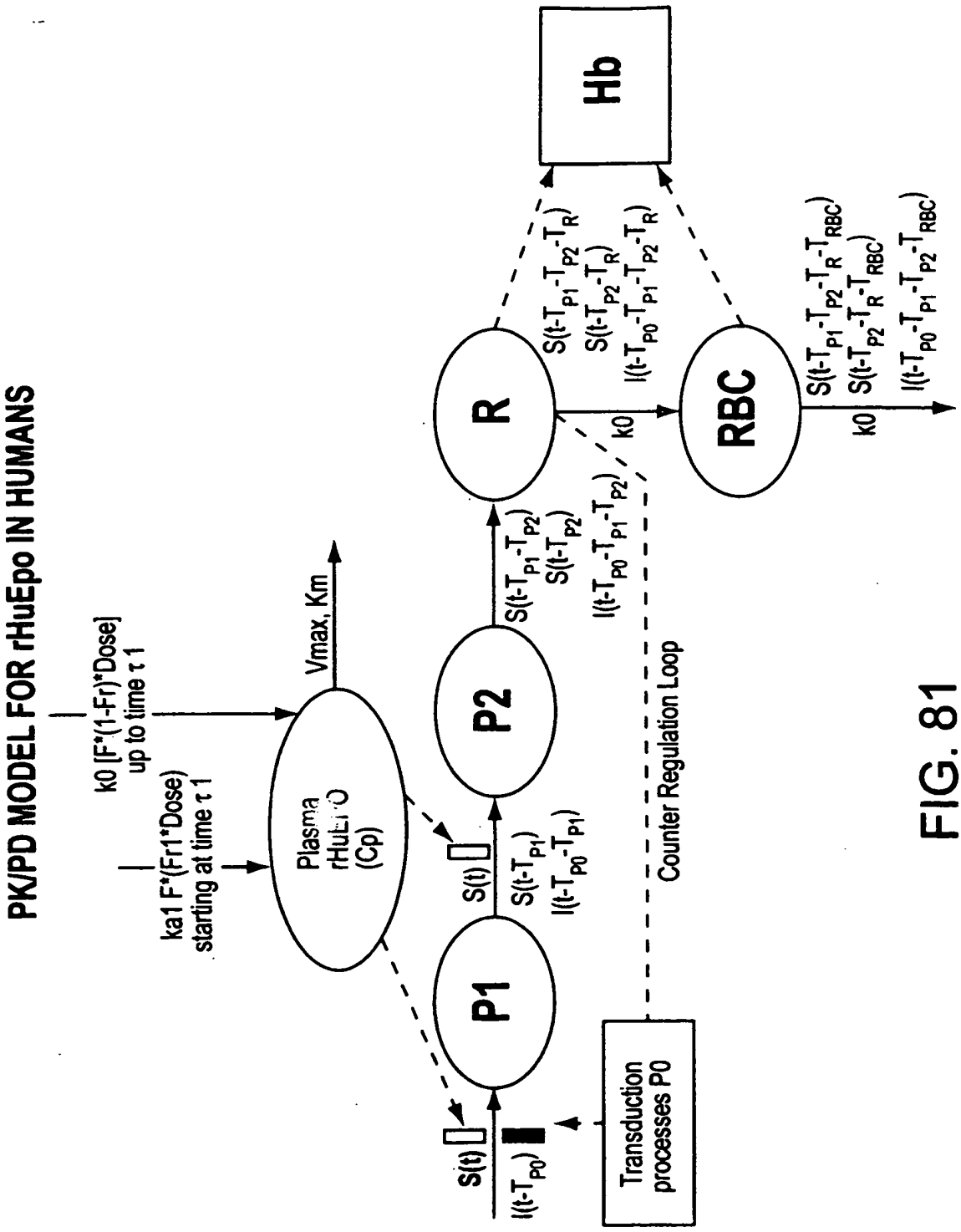

PK/PD MODEL FOR rHuEpo IN HUMANS
k0 [F*(1-Fr)*Dose]
up to time τ 1
ka1 F*(Fr1*Dose)
starting at time τ 1
Plasma
rHuEPO
(Cp)
Vmax, Km
P1
P2
R
RBC
Hb
S(t)
I(t-T_P0)
S(t-T_P1)
I(t-T_P0-T_P1)
S(t-T_P1-T_P2)
S(t-T_P2)
I(t-T_P0-T_P1-T_P2)
S(t-T_P1-T_P2-T_R)
S(t-T_P2-T_R)
I(t-T_P0-T_P1-T_P2-T_R)
S(t-T_P1-T_P2-T_R-T_RBC)
S(t-T_P2-T_R-T_RBC)
I(t-T_P0-T_P1-T_P2-T_RBC)
k0
Transduction
processes P0
Counter Regulation Loop

FIG. 81